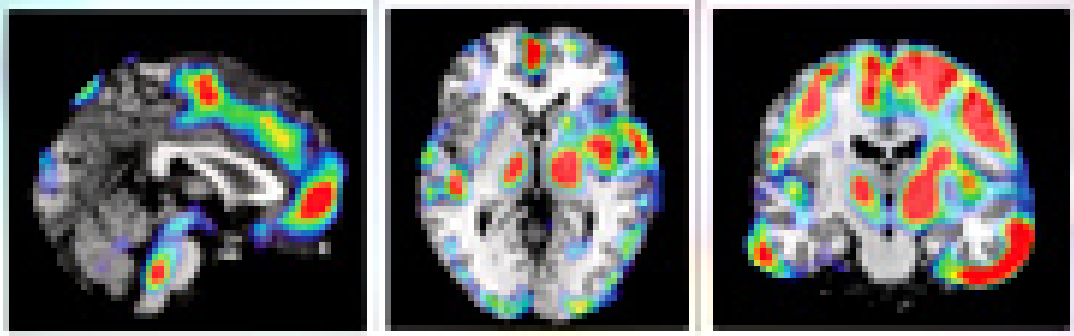

PRINCIPLES AND PRACTICE OF

GERIATRIC SLEEP MEDICINE

EDITED BY
S. R. PANDI-PERUMAL
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Medicine

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Principles and Practice of Geriatric Sleep Medicine

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Dedicated to our wives and families for making our lives special and all our efforts worthwhile

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Foreword

There is no question that we live in a world increasingly filled with multiple, contradictory, and rapidly changing stimuli. The invention of artificial lighting in the nineteenth century improved and transformed the lives of millions, as well as the later inventions of television, the personal computer, and the Internet, all serving as risk factors leading to decreased sleep. We now have the high-intensity, 24/7 world. It is becoming evident that the great technological and social changes that now characterize modern life have contributed also, at least somewhat, to the increasing incidence of sleep disorders.

In the last 30 years sleep medicine has begun to flourish, with greater interest being shown by clinicians in sleep disorders and increasingly larger numbers of research grants being given to study them. These developments have greatly enhanced our understanding of the reciprocal causal relationship that exists between disease and sleep.

At the same time, population aging and longevity have increased. In the twentieth century people living in the developed world gained some 30 additional years of life, a sudden extension of the human lifespan, which was greater than had been attained during the preceding 5000 years of human history. As people have begun to live longer, especially after 50 years of age, the problems of achieving restorative or even minimally adequate sleep has become an important life concern. As individuals age they increasingly face problems related to getting to sleep, staying asleep, achieving deep, restful sleep, and waking up at normal times. The problem of disrupted sleep and its sequelae for overall health has now led to the development of the new field of geriatric sleep medicine.

This book *The Principles and Practice of Geriatric Sleep Medicine* provides an overview of this important and complex subject with contributions from authors from around the world. It begins with a review of the important changes in circadian rhythm in aging. It places into context the significance of the middle-age transition to old age and the impact of Alzheimer's disease. The volume has also attempted to address practical issues that inevitably come to the attention of clinicians but which also have a broader social impact, namely, life adjustment issues and traffic safety of older persons. It covers major diseases of old age in nursing home residents. It ends with important therapeutic considerations.

Robert N. Butler
New York

Preface

Sleep is essential to our well-being and occupies about a third of our lives. When deprived of an adequate amount of sleep, individuals are subject to fatigue, clouded thinking, and possible metabolic dysregulation leading to diabetes and obesity, and to a diminished quality of life. For older people, these symptoms can be more than a matter of discomfort; they can lead to more serious complications. Falls resulting from fatigue and confusion, for example, can result in debilitating, costly injuries in this vulnerable population. The importance of recognizing and treating age-associated health problems, such as sleep disorders, takes on a new meaning as the nation's elderly population grows to record numbers. Despite the widely held view that sleep difficulties are a normal accompaniment of the aging process there are, in fact, many healthy older adults who report few or no sleep problems. Sleep patterns change with age, but disturbed sleep and waking up tired every day are not part of normal aging. For many among the older population, the root causes of disturbed sleep are the various underlying medical and social problems that also tend to increase as people grow older. Apart from the symptomatic effects of illness or life stressors on sleep, there are nevertheless normal developmental changes in sleep that occur with advancing age. An understanding of these changes will hopefully lead to advances in current techniques for preventing or reducing the economic and social impact of these changes in the older population

The Institute of Medicine report ("Sleep Disorders and Sleep Deprivation: An Unmet Public Health Problem"), issued in 2006, estimated that 50 to 70 million Americans chronically suffer from sleep disorders that interfere with their daily functioning and adversely impact their health and quality of life (QoL). These often go unrecognized and/or are treated inappropriately. It has been estimated that over 50% of older Americans have some chronic sleep problem. The American population aged 65 years and older now constitute about 13% of the population and is projected to increase to over 20% of the population by the middle of the twenty-first century. The increase in the older populations is seen world-wide and reflects the "squaring" of the population distribution. In fact, the World Health Organization projects that by 2015, the proportion of people 65 years and older in the world will exceed those younger than 5 years of age.

Sleep disorders become increasingly common in later life, and are often co-morbid with other age-related health problems. Complaints about sleep in general increase with age, as do specific complaints of insomnia. Estimates of the prevalence of insomnia in the elderly vary widely depending upon the definition of insomnia and the method of assessment used. In one study conducted by the National Institute on Aging (NIA) on over 10 000 older adults living in the USA, 28% of the respondents reported difficulty falling asleep, and 42% reported both difficulty falling asleep and difficulty staying asleep, and it has been estimated that over 50% of people 65 years and older had at least one chronic sleep complaint (Foley *et al*., 1995). At a 3-year follow-up, 15% of the individuals with sleep complaints at the initial interview did not report sleep difficulties, and 5% of those without sleep complaints at the initial interview complained of difficulties 3 years later (Foley *et al*., 1999). Further analyses of these data showed that only 5.8% of individuals without risk factors for insomnia, identified as medical, psychosocial or psychiatric difficulties, at the initial visit, reported new insomnia at follow-up. These data suggest that sleep complaints are generally quite common in older adults, that developing new difficulties with sleep is associated with poor health or psychological factors, and that resolving sleep difficulty is related to better health quality. The result of 1000 telephone interviews of randomly selected adults in the USA indicated that the prevalence of occasional insomnia did not change with age; however, the prevalence of chronic insomnia was highest (20%) in adults age 65 and over (Ancoli-Israel and Roth, 1999). This

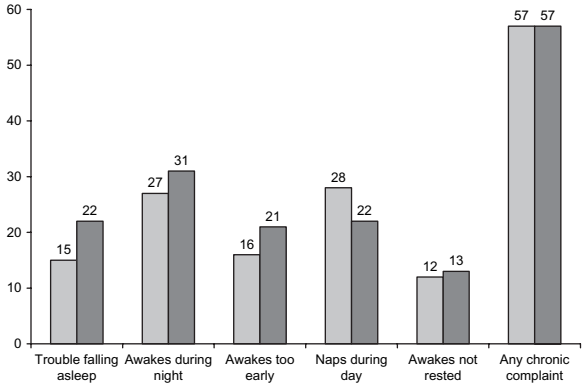

Figure 1. Percent distribution of sleep complaints (Foley *et al*., 1995). Left bars are men and right bars are women.

suggests that, although occasional sleep complaints may not be associated with age, older adults experience chronic sleep difficulties more often than younger adults.

Older individuals usually take multiple medications, some of which may interfere with their sleep, and often use hypnotics and over-the-counter drugs to deal with their sleep problems. Further, with advancing age the body undergoes a number of physiological changes and associated stresses. Among these are changes in homeostatic and circadian processes, responses to drugs and their metabolism, changes in their hormonal levels, cardiovascular and metabolic diseases, and sensory changes, all of which can adversely affect sleep. The proportion of commonly reported sleep problems also changes as people age. Several sleep disorders that are more prevalent in the older population include co-morbid insomnia, sleep disordered breathing, restless legs syndrome, advanced sleep phase syndrome, and disordered sleep associated with neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease.

Several therapeutic strategies have been employed in treating sleep disorders, particularly insomnia. These include but are not limited to pharmacostrategies using recently introduced melatonergic agonists such as Ramelteon as well as chronotherapeutic interventions involving the delivery of drugs at strategic times. Much work remains to be done in testing the safety and efficacy among older subjects of these recently introduced pharmaceuticals. Other non-pharmacological alternative and cognitive behavioral therapies, such as bed restriction, behavioral modification, sleep hygiene, etc., can also play critical roles in the treatment and management of age-related sleep disorders. The evidence reviewed in this volume supports the conclusion that sleep disorders are closely linked to overall health and that efforts aimed at reducing these disorders can reduce the severity of other health problems. This evidence further supports the inference that the prevention and treatment of sleep difficulties in the elderly has significant implications not only for the affected individuals, but also for care-givers and for the nation's public health concerns generally.

The editors of the present volume have assembled chapters that summarize and review some of the latest discoveries concerning basic and clinical aspects of geriatric sleep medicine. To this end a number of outstanding contributions have been sought from acknowledged experts in their respective fields. This volume also recognizes that a broad range of factors influence sleep in the elderly. The editors' goal therefore has been to present the more recent developments in the fields of sleep and geriatrics, and to provide a context for considering them both in depth and from a multidisciplinary perspective. This volume thus brings together the expertise of clinicians and basic researchers representing a range of interests in neuroscience, neuropharmacology, sleep physiology, and biological rhythms.

S. R. Pandi-Perumal
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Andrew A. Monjan

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Credits and acknowledgments

This volume owes its final shape and form to the assistance and hard work of many talented people. Creating a book, which surveys a broadly interdisciplinary field such as sleep and geriatric medicine, involves the collaborative scholarship of many individuals. We express our profound gratitude to the many people who have helped and also to some who have contributed without realizing just how helpful they have been.

Our sincere appreciation goes to Dr. Butler, who graciously agreed to write the Foreword. We wish to express our appreciation for his contribution.

The editors wish to express their sincere appreciation and owe endless gratitude to all our distinguished contributors for their scholarly contributions that facilitated the development of this volume. Our largest debt obviously goes to our outstanding authors who, regardless of how busy they were, managed to find time for this project. They, in a most diligent and thoughtful way, have brought a wide range of interests and disciplines to this volume entitled *Principles and Practice of Geriatric Sleep Medicine.* They accepted our submission deadlines and tolerated with great patience our repeated requests on special formatting requirements, our frequent phone calls, and our bombardment with high-priority email messages.

It is of course a pleasure to thank our many colleagues who commented on individual chapters and have provided invaluable suggestions: we are indebted to them all. A very special debt of gratitude and appreciation is owed to the several reviewers who made numerous helpful suggestions. Their candid comments and insights were invaluable.

We would like to thank the secretarial and administrative staff of our respective institutions for helping us to stay on task, and for their attention to detail.

No volume can be completed without the untiring efforts of many publishing professionals. Producing a volume such as this is a team effort and we acknowledge with gratitude the work of the editorial department of Cambridge University Press. We are especially indebted to Mr. Nicholas Dunton, Senior Commissioning Editor – Medicine, who was an enthusiastic and instrumental supporter from the start to the end. Our profound gratitude is offered also to Ms. Katie James, Editor – Medicine, whose equally dedicated efforts promoted a smooth completion of this important project. Both Nick and Katie provided unflagging dedication, invaluable help, and encouragement. We appreciate their intellectual rigor and personal commitment on our project.

We also thank the Cambridge University Press production department colleagues for their meticulous work. They all gave unstintingly of their time, energy, and enthusiasm. This talented and dedicated team of copy and production editors strengthened, polished, trimmed, and conscientiously checked the text for errors.

We have thoroughly enjoyed efficient help and invaluable advice and constant interactions with the editorial staff at Cambridge University Press, who also deserve special recognition and thanks: Dawn Preston and the entire production and marketing staff. They supported us unreservedly and helped us to focus on our targets. They also patiently acknowledged our requests for extensions of deadlines and last-minute changes while bringing the volume to press. They were even willing to do this painstaking work in the final month of preparation. They, along with other members of the production team, were unflaggingly dedicated to shepherding this volume through its various stages, copy-editing the manuscript, designing the text, preparing the index, and designing the striking cover.

The editors would also like to acknowledge the close co-operation we have received from each other. We think we made a good team, even if we say it ourselves!

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this process could have been incomplete. Thus, if any copyrights have been overlooked, the publisher will ensure correction at the first opportunity for subsequent reprint of this volume.

Last, but certainly not least, we are most grateful to our wonderful wives and families, who provided love and support too valuable to measure. We owe everything to them. Their understanding and patience, wisdom, creativity, constant support, and encouragement while the book was being developed are immeasurably appreciated. Without the love and support of our families and friends, we could not have completed this project. Being able to spend more time with them is our chief reward for finishing. They saw the work through from the conception of an idea to the completion of an interesting project with unwavering optimism and encouragement. They were the source of joy and inspiration for us, and we thank them for their continuing support, and for understanding the realities of academic life!

Without a whole host of dedicated individuals, thus, this volume would have never come to completion. All of the above experts made this volume possible. We recognize them individually and collectively for their contribution. To all these people goes our sincere gratitude. To all the people who contributed to this project we want to say "thank you!." Their willingness to contribute their time and expertise made this work possible, and it is to them that the greatest thanks are due. They made our work possible and pleasurable.

For this, and for so much else, we are ever grateful.

Organization of the first edition

Users of this first edition of this volume will find that it is divided into four major sections: Part 1: Sleep and normal aging; Part 2: Neuroendocrine and homeostatic changes in the elderly; Part 3: Sleep disorders in the elderly; and Part 4: Treatment of sleep disorders in the elderly.

In its 41 chapters, this volume covers a broad range of abnormalities that are associated with sleep in the elderly. Many of the topics relate to problems encountered in clinical practice, while others deal with the more basic foundations of sleep disorders as these are viewed from the perspectives of neuropharmacology and neuropsychology. The volume begins with a review of various practical matters such as sleep complaints and sleepiness. An extensive section deals with one of the most common groups of disorders seen at all levels of medical care, namely, the insomnias. Following this, the therapeutic efficacies of a wide range of pharmacological agents as well as the major approaches to sleep therapy are overviewed.

Part 1 comprises of an overview of the circadian timing system in the elderly: in it are reviewed the age-related changes occurring in the pharyngeal structure and function in normal versus apneic subjects, gender-related sleep issues such as menopause transition and post-menopausal conditions, sleep and memory, and sleep in middle-aged subjects.

Part 2 addresses the neuroendocrine and homeostatic changes associated with advanced aging. This section also addresses the role of melatonin in aging and Alzheimer's disease.

Part 3 addresses the sleep disorders that are commonly present in the elderly population. This section starts with the epidemiology and assessment of the autonomic dysregulation that occurs during sleep among the elderly. Readers should also find useful the in-depth coverage of topics such as circadian rhythm dysregulation in the elderly, and the roles played in its etiology by advanced sleep phase syndrome (ASPS), shift work, and Alzheimer's disease. Other sleep-related disorders such as nocturia, co-morbid medical conditions such as fibromyalgia, obesity, pain, stroke, and cardiovascular complications, and mental conditions such as anxiety and depression are also covered.

Topics such as sleep and Parkinson's disease, insomnia, narcolepsy, movement disorders, rapid eye movement (REM) sleep behavior disorder, sleep apnea and sleep disordered breathing, sleep in the institutionalized elderly, and sleep in care-givers are reviewed.

Special attention is also given to the effects of fatigue and sleepiness in the elderly and how such risk factors can be managed effectively. This section also discusses the importance of sleep, sleepiness, and their effects on traffic safety in elderly subjects. Other topics include the relationship between sleep and falls and dreaming disorders in the elderly population.

Part 4 includes the treatment of sleep disorders in the elderly; readers are given an overview of geriatric psychopharmacology as well the pharmacological treatment of elderly patients. The risks and benefits of benzodiazepine (BZD) use in the elderly population are considered. Non-pharmacological (cognitive-behavioral) and self-help treatments of primary and co-morbid insomnia in the elderly are also reviewed. Also covered in this part are the epidemiology and use of various medications, including complementary and alternative medicine (CAM) therapies, and their effects on sleep along with the therapeutic benefits of naps and light therapy in the aging population. Finally, this section addresses the role of neuroimaging as an adjunctive tool for treating sleep disorders in the elderly.

The editors of this volume have been fortunate to obtain commitments from leading experts in geriatric sleep medicine to contribute detailed reviews on their topics of expertise, backed up by extensive bibliographies. Inevitably there has been an overlap of information in some of the reviewed material, and occasionally a few gapshave remained despite the

substantial contributions made by experts in each field. The people we approached are by definition busy people, and we are wholeheartedly grateful to them for giving up so much time to contribute.

It is our hope that this effort has succeeded in its goal of providing a thoughtful balance of basic experimental and clinical viewpoints, and further that it will serve as a foundation for understanding and ultimately treating sleep disorders in the elderly.

It has been our goal to provide a concise yet comprehensive review of the expanding and increasingly multidisciplinary area of geriatric sleep medicine. Inasmuch as we envision continuing updates of this volume, readers are also encouraged to contact us with any thoughts and suggestions for topics to be included in future editions. We welcome communication from our readers concerning this volume and its organization, and especially concerning any inaccuracies or omissions that remain. We take full responsibility for any such inaccuracies, and we appreciate having them drawn to our attention.

In summary, this volume addresses sleep disorders in the elderly from multiple perspectives. Because this volume is primarily written for clinicians and medical students, it emphasizes the clinical features of the various sleep disorders and therapeutic options that have been developed to treat them.

It is our hope that this volume will enable interested scientific and medical researchers to develop a better understanding of the scope in the science and practice of geriatric sleep medicine. We also hope that this volume will generate new ideas that lead to improvements in the care of geriatric patients who suffer from sleep disorders.

S. R. Pandi-Perumal
Jaime M. Monti
Andrew A. Monjan

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Andrew A. Monjan, PhD, MPH was the Chief of the Neurobiology of Aging Branch of the Division of Neuroscience within the National Institute on Aging prior to his retirement. His duties included the development and monitoring of research on brain–behavior interactions in the aging process and their underlying cellular and molecular processes. Sleep research was an important priority within this program, and Dr. Monjan has served as the Executive Secretary of the National Commission on Sleep Disorders Research. He has received a number of NIH Directors' Awards for his meritorious service, and a special recognition award from the Sleep Research Society for his work in furthering research into sleep and aging.

Part 1 Sleep and normal aging

Aging and circadian rhythms: general trends

S. R. Pandi-Perumal, D. Warren Spence, and Vijay Kumar Sharma

Introduction

Age-related changes in circadian rhythms occur in both animals and humans [1, 2, 3, 4]. It is also known that dysregulated circadian rhythms are a major cause of sleep pathology, and thus there tends to be a strong correlation between increasingly disrupted sleep patterns and advancing age. Circadian rhythms, which have a periodicity of approximately 24 hours (circa = about; dies = day), have been shown to have survival value [5, 6]. The progressive deterioration in functional vigor, the most pronounced hallmark of aging, is believed to be due to the loss of co-ordination between interdependent oscillatory processes. These processes become increasingly dissociated (*disphasia*) with age [7]. According to Samis, this disphasic condition is the consequence of aging because the aging organism has lost much of its adaptive resiliency, even though the diphasic episodes may occur only briefly or occasionally a complete re-entrainment of the aberrant rhythms does not occur. Small changes therefore have large consequences. Only a slight discrepancy between the diphasic rhythms and compensatory re-entrainment will, with time, produce increasing randomization in the affected processes.

Aging and circadian rhythms

There are many age-related changes that affect circadian rhythms. It is generally believed that age-associated circadian disruption occurs at various levels of biological organization. These age-related disruptions have been studied in laboratory animals and have been extensively reviewed in the literature [8, 9, 10, 11, 12, 13]. Such age-attenuated changes have been associated with several neural, endocrine, metabolic, and behavioral rhythms in animals [2, 3], and are closely linked to the period of the circadian pacemaker which controls these rhythms [14]. Indeed, anatomical and electrophysiological studies have shown that age-related changes occur within the suprachiasmatic nucleus (SCN, the mammalian "biological clock"), and that these changes occur in both humans and other mammals [15, 16, 17, 18, 19, 20, 21, 22].

Aging is often accompanied by reductions in the nocturnal melatonin and pineal *N*-acetyltransferase (NAT) rhythms [23, 24]. Additionally, aging is associated with a general decline in body temperature [25, 26], as well as reduction in the amplitude of light-induced phase response curve (PRC) [14]. Older animals take longer to re-entrain to phase-shifted light/dark (LD) cycles compared to their younger counterparts [27]. Further, there is a general tendency towards sleep loss during the day. The fact that older animals sleep less during the day (the sleep period of rats) suggests that it is a selective loss of sleep that accounts for the largest component of age-related reduction in total sleep time (TST).

Various systematic changes occur in rhythmic processes as organisms age. While these modifications may generally reflect the normal aging process, it is apparent that individual differences exist in the way that aging progresses. As a result, many attributes of normal development show a characteristic progression towards circadian disorganization, as manifested by increases in the standard deviations (SD) of their measured values.

Numerous changes in overt rhythmicity appear to be associated with aging [2, 3, 28]. Some of these have been attributed to deterioration in the functioning of circadian pacemakers, while others may result from a general decline in the capacity for entrainment ability and/or in the systemic processes that are clock controlled.

Observed changes in overt circadian patterns include:

(1) Reduction in the amplitude of rhythms [14], fragmentation of rhythms, and disorganization in their temporal order, vigor, and precision [7, 9, 10, 29, 30, 31];

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(2) Loss of entrainment stability and responsiveness to zeitgebers [31]; and
(3) Changes in clock period and stability.

In addition, alterations in the clock-regulated processes are seen. These include changes in the level of specific activities, in the temporal distribution of behaviors, in the levels of circulating hormones, and in the density of certain peptides, neurotransmitters, and receptors [32].

Amplitude and organization

Decrease in the amplitude of rhythmic functions reflect a general loss of their "stability" or robustness [33]. The relationship between rhythm disturbances and aging has been discussed extensively in several reviews [2, 3, 9, 10, 12]. It has been reported in numerous studies that as aging progresses there is a general deterioration of wheel running activity of rodents [30, 34, 35, 36, 37, 38].

However, in 1998 Davis and Viswanathan [38] did show that the free-running period of Syrian hamsters remained stable throughout their lifespan. Generally, aging is associated with increasingly disruptive changes in circadian rhythms. Age-related disturbances in the locomotor activity of humans, for instance, have been observed [39]. In addition, aging is associated with a reduction in the amplitude of other behavioral rhythms, including feeding, drinking [40], and sleep/wake cycles [41, 42].

In addition to behavioral changes, physiological rhythms are also affected during the aging process. This includes rhythms in body temperature (mice and rats), audiogenic convulsions (mouse), and oxygen consumption (mouse), as well as the excretion of potassium (humans), growth hormone (GH; human), testosterone, and leutenizing hormone (LH; humans) [6, 12, 25, 26, 43, 44, 45, 46, 47]. In 1982 Halberg reported that circadian rhythms of cortisol, aldosterone, prolactin, and GH in the blood plasma are altered in older human subjects [48]. Age-related changes have also been noted in the circadian hormonal rhythms of other mammals. For instance, epinephrine (E) and norepinephrine (NE) have been shown to undergo an age-related decline in circadian amplitude and mesor, without any apparent change in the acrophase [48].

It is difficult to assess to what extent a decrease in the amplitude of overt rhythms reflects changes in circadian pacemaker activity as opposed to parallel age-dependent losses of peripheral function. Satinoff *et al.* (1993) demonstrated that the SCN of older rats exhibits disturbed patterns and lower amplitude neuronal firing compared to younger animals (although their behavioral rhythms were not always disturbed) [19]. Wise *et al.* showed that there is a decrease in the SCN glucose utilization in older rats in response to LD transitions [18, 49]. There are also numerous reports of age-related changes in the structure and neurochemistry of the SCN, including alterations in the cells producing vasopressin (AVP) [15, 16, 21] and vasoactive intestinal polypeptide (VIP) [17, 50, 51]. While these alterations do not always correlate with overt changes in behavior and physiology [16, 52, 53], there is sufficient evidence for differences in the SCN of younger and older animals to suggest that a link exists between the functional impairment of the "master" circadian pacemaker (SCN) and observed changes in the overt circadian patterns. Moreover, the re-consolidation of the host-driven locomotor activity rhythm following SCN transplantation in older hamsters suggests that the SCN plays a primary role in maintaining temporal organization in metabolic functions in mammals [54].

A predictable consequence of the reduction in rhythm amplitude is a loss of synchrony or inappropriate phase-relationships among constituent circadian rhythms. It has been asserted that the primary function of biological clocks is to produce temporal organization among rhythmic processes, and to entrain them to appropriate environmental cycles. It is predictable, therefore, that if circadian clocks or their control mechanisms become impaired, this organization will be compromised. Disorganization generally appears as changes in the temporal structure of the organism's rhythmic physiology and behavior. Rhythms remain synchronized with each other but may assume inappropriate or variable phase relationships [7]. Such disorganization is well documented in humans [41, 55, 56].

Age-related changes in the amplitude of many physiological and behavioral rhythms have been noted in the rest/activity cycle, core body temperature (cBT), feeding, drinking, eating, and an organism's response to LD cycles. Such reductions in the amplitude of behavioral rhythms are quite similar to those observed in sleep/wake cycles.

Entrainment and responsiveness to zeitgebers

In most studies, rhythms in aged organisms are measured in 24-hour LD cycles, so that inappropriate phase

relationships with the environment can be detected. A common example of this is seen in elderly humans, in whom sleep/wake patterns become disorganized and variable compared to those of young adults [41]. In LD cycles, loss of temporal organization could result from either impairment of clock function, and/or due to a reduction in its sensitivity to zeitgebers. The primary zeitgeber for most organisms is the LD cycle; however, there is some evidence that other rhythmic factors in the environment can also assume this role [57], and it is almost certain, for instance, that non-photic stimuli can alter rhythms, and thus can act as zeitgebers [58, 59].

Entrainment to LD cycles is a key feature of circadian clocks, and is known to be affected by age-dependent changes in period and photic sensitivity. However, entrainment of circadian clocks is also affected by the organism's acute responses to light that may mask circadian gating. The simplest experiments for examining circadian responses to environmental stimulation have involved re-entrainment and phase-resetting paradigms. While there appear to be changes in these responses during aging, it is not consistent across species or even among experiments. For example, Rosenberg *et al.* reported that older rats take longer to respond to a phase-reversal in the LD cycles as compared to their younger counterparts [27]. On the other hand, Peng *et al.* reported that there is no difference between young and old rats in their rates of re-entrainment [40]. Zee *et al.* [60] found that it takes more time for younger hamsters to re-entrain to a phase-advanced LD cycle, but less time when the cycle is phase delayed, whereas Valentinuzzi *et al.* [37] reported that re-entrainment in old mice is accelerated when the LD cycles are phase advanced but remains unchanged when the LD cycles are phase delayed. The magnitude of light-induced phase delays increases with age in rats [61], but decreases with age in mice [62] and in hamsters [14]. Such changes, however, can be reversed by the use of bright light pulses [61, 63].

The reasons for these disparate findings are not known. Because different species have been used in separate experiments, and because experimental conditions change from laboratory to laboratory, such differences in findings may not be surprising. However, it is also possible that such discrepancies are related to the fact that there are fundamental inter- and intra-species specific differences in the way animals age. For example, some hamsters lose their highly consolidated pattern of wheel running behavior as they age, while others do not [64]. Because activity influences the circadian responses to light [65], and can also influence directly the phase and period of circadian rhythms, aging may have different effects on rhythmicity due to different changes in activity patterns.

Responses to non-photic signals are also affected by age. Phase-shifts induced by a serotonin (5-HT) agonist [66] or by the benzodiazepine (BZD) triazolam are reduced in aged hamsters [67]. The latter effect can be reversed by transplantation of a fetal SCN [68], and by a melatonin agonist [69]. Melatonin can also facilitate re-entrainment to a shifted LD cycle [70].

Age-related changes in circadian organization

The most prominent age-related changes in circadian behavioral rhythms are those observed in free-running and entrained rhythms. Pittendrigh and Daan found that the free-running period decreases in rodents from puberty to old age [30]. With regard to entrained rhythms, Weitzman *et al.* proposed that changes in the relationship between endogenous rhythms and environmental rhythms accounted for the deficits in circadian organization that are known to occur in advancing age [41].

Discrepancies in the age-related changes in period length

It should be noted that several discrepancies exist in the findings from studies on age-related changes in period length. There are many schools of thought regarding the interpretation of these changes. Several studies observed decreases in period length [10, 30, 41, 71], whereas other prominent studies observed increases [11, 37, 72, 73, 74]. Some researchers argued that, in fact, negligible changes in circadian period occur with age [75]. According to Sharma and Chandrashekaran, the differences in the reported findings on age-related period changes can be attributed to the fact that in several studies rhythms were not monitored for a long enough period and the observations were made on animals maintained under different LD conditions [75]. Czeisler *et al.* also concluded, based on their forced desynchrony protocol studies, that circadian period does not shorten reliably with age [76]. Because there is such a range of effects reported, it seems unwise at this point in time to make

any definitive statements about systematic changes in circadian systems that occur with age. It may be possible that variability in circadian function increases in conjunction with variability in an individual's behavioral pattern. Thus, in contrast to elderly subjects who are healthy, and who often show greater regularity in the timing of their activities (possibly as an adaptive behavior to overcome a less robust circadian timing system [83]), demented elderly patients show a marked loss of stability.

Modifications in circadian rhythms with aging

The amplitude of many intrinsic rhythms decreases with age, with an apparent decrease in the "maxima" for the rhythm. As summarized by Davis, these rhythms include those in body temperature (mouse and rat), audiogenic convulsions (mouse), oxygen consumption (mouse), potassium excretion (humans), growth hormone (human), testosterone (human), and leutenizing hormone concentration (humans) [6].

Under constant darkness, circadian rhythms "free-run" with an intrinsic (genetically determined) period (τ; tau) that is either slightly longer or slightly shorter than 24 hours. The average human τ is believed to be in the range of 24.2 to 24.4 hours. In the elderly, however, the value of τ decreases with age, though only by a small degree [2, 3, 14, 29, 30, 60, 61]. As the value of τ increases or decreases, there is also an associated increase in its standard deviation. For example, some species exhibit an age-related lengthening of τ, while other species show an age-related shortening of τ [74, 77, 78, 79].

Studies carried out by Davis and Viswanathan, Sharma and Chandrashekaran, and Czeisler *et al.* found that τ remained relatively stable over the lifespan of the animals investigated [38, 75, 76]. Studies by Valentinuzzi *et al.* and Kendall *et al.* suggested that the clock period increases as the animals aged [37, 80]. However, these increases were attributed to the methodological differences such as a restriction in the range of ages studied, after-effects of previous entrainment, and/or activity feedback in the circadian pacemaker [80].

Irregular circadian rhythms with age-related neurodegenerative disease

As is evident from this overview, age-related changes in circadian organization can be seen in many rhythm parameters, including their phase-relationship, amplitude, period, and entrainability. Van Someren and co-workers have pointed out the importance of investigating not only these parameters, but also their inherent variability over subsequent days. They provided methods for quantifying such variability, and found evidence for a specific loss of stability over days in the rest–activity rhythm of elderly patients suffering from Alzheimer's dementia [81, 82]. Thus, in contrast to elderly subjects who are healthy, and who often show greater regularity in the timing of their activities (possibly as an adaptive behavior to overcome a less robust circadian timing system [83]), demented elderly patients show a marked loss of stability in their temporal organization. It is likely that such poor stability in demented elderly patients contributes to both nocturnal sleep problems and diurnal sleepiness, as has been demonstrated experimentally in young adults [84, 85]. Moreover, poor stability may also contribute to the neuropathological changes in the medial temporal lobe area, and in the associated memory problems that are typical of Alzheimer's disease, a phenomenon that has been demonstrated in young adults who show irregular synchronization to the environmental LD cycle due to occupational demands [86, 87, 88]. For this reason, the application of whole-day bright light exposure has been effectively used as a practical intervention for improving the stability of rest–activity rhythms in demented elderly patients [89]. Moreover, preliminary data suggest that long-term application of such a therapeutic zeitgeber enhancement indeed attenuates cognitive decline [90].

Summary

In this chapter, we have cited evidence showing that circadian rhythms have a tendency to become less robust with increasing age, i.e. they generally exhibit decreases in amplitude and less stability. Some obvious consequences of such reductions in rhythm amplitude are fragmentation of rhythms, complete loss of temporal order and structure, loss of stability of entrainment and responsiveness to zeitgebers, changes in clock period and its stability, and inappropriate phase relationships among behavioral and metabolic oscillations.

Age-related decreases in the amplitude of circadian rhythms in humans and other mammals have been linked to a deterioration of rhythmic behaviors such as those seen in locomotor activity, feeding, drinking,

and sleep and wakefulness. While some of these changes are due to molecular and physiological changes in the circadian pacemakers, others stem from a general decline in entrainment mechanisms or clock-controlled processes. Anatomical and electrophysiological studies have shown that age-related changes occur within the biological clocks of mammals including humans. The SCN of aged animals have abnormal patterns and lower amplitude of neuronal firing compared to young animals, and there is a decrease in SCN glucose utilization in aged rats. There is increasing evidence for age-related changes in the structure and neurochemistry of the SCN, including alterations in cells producing vasopressin.

Many attributes of normal aging and development show a characteristic progression towards circadian disorganization, of which the most undesirable consequence, from the clock's perspective, is disturbances in the sleep/wake cycle. The translational aspect of such observations is that many of the findings related to animals show similarities to the findings in humans. In essence, disruption in rhythm, whether of shorter or longer duration of time, will have undesirable consequences for health and well-being. In general, circadian rhythms have a tendency to become less robust with advancing age, i.e. they show a decrease in amplitude and/or are phase advanced [10]. Moreover, an age-associated shortening or speeding up of the clock, which reflects phase advancement of the sleep/wake cycle, can produce changes in habitual bedtimes and awakening times in the elderly. Such phase advances may be related to changes in the core body temperature (cBT) rhythm that shows amplitude attenuation and phase advances [91]. Further, major age-related alterations in temporal organization result in a shortening of the circadian period of waking and of paradoxical sleep (PS) – a deep sleep with a brain wave pattern more like that of waking states than that of other states of sleep, which occurs during rapid eye movement (REM) sleep [92].

The fact that changes occur in the sleep/wake cycle (increased wakefulness at night and increased sleepiness during the day) suggests that aging is associated with desynchronization of circadian rhythms [93]. Arguably, some of the sleep dysfunctions experienced by certain aged individuals are due to insufficient exposure to zeitgebers (environmental time cues, such as the daily changes in luminance from sunlight), particularly among those who are house-bound or institutionalized [94].

There is also evidence that the rest–activity rhythms of the elderly suffering from Alzheimer's dementia show a general loss of stability with age. It is likely that such poor stability in demented elderly patients contributes to both nocturnal sleeping problems and diurnal sleepiness, and to the neuropathological changes in the medial temporal lobe area and

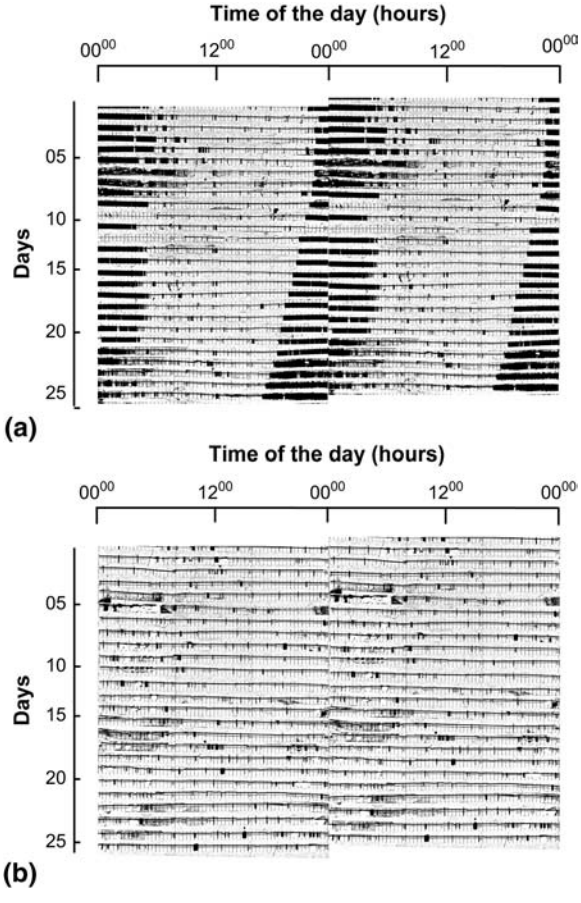

Figure 1.1. Locomotor activity data illustrating activity/rest profile of (a) young (~4 month old) and (b) old (~18 months) field mouse *Mus booduga*. The locomotor activity of the animal was monitored using an activity running wheel (diameter ≈ 20 cm) attached to a transparent plexiglas cage of dimension 0.07 m × 0.11 m × 0.09 m, with a small opening of 0.02 m diameter. Reed-relays attached to the wheels activated the writing stylets of an Esterline Angus A620X Event Recorder when the running mice caused revolutions of the wheel. The activity patterns of as many as 18 mice in separate running wheels, placed on open shelves in the experimental room, could be assayed concurrently in constant darkness. The temperature inside the experimental rooms (3.05 m × 2.44 m × 4.01 m), which did not have windows but were gently ventilated, remained constant at 25 ± 1°C and the relative humidity was 75 ± 5 %. Food (millet and grain) and water were available *ad libitum*. Actograms were obtained by pasting 24 hr activity/ rest strips chronologically one below the other in the standard manner and double plotted.

the associated memory problems that are typical of Alzheimer's disease. For this reason, the application of bright light exposure has been effectively used as a practical intervention for improving the stability of rest–activity rhythms in demented elderly patients [88, 95] and general well being [96].

Table 1.1. Summary of some of the age-related changes in circadian rhythm in animals: changes in general characteristics

Criteria	Comments	Reference(s)
Precision	The day-to-day stability of the different sleep states is reduced in old rats, whereas that of the drinking rhythm is enhanced	79
Impairment of rhythm	Age-related deficits in learning and memory, changes in emotional behavior, and abnormality of circadian rhythms in mice. In aged animals, endothelial NO synthase activity was markedly decreased during the daytime, along with impairment of clock gene expression and the circadian variation in blood pressure	97, 98, 99, 100, 101, 102
Internal desynchronization	Activity and core body temperature rhythms dissociate with aging	102, 103
Light/dark (LD) activity difference	Age-related changes include decrease of wheel-running activity, decrease in circadian rhythm amplitude, increase in proportion of light activity, and increase in split activity rhythms	102, 104, 105, 106, 107, 108, 109
Rate of resynchronization	Old animals take significantly longer to re-entrain compared to younger ones. Resynchronization is significantly slower in old mice. Middle-aged hamsters resynchronized more rapidly after a phase advance in LD cycle than young hamsters, whereas young hamsters phase delay more rapidly than middle-aged hamsters. Following an advance of the LD cycle, circadian rhythms in the pineal NAT activity and melatonin content reappeared in young rats, but was abolished in old rats	37, 60, 110, 111, 112
Circadian period (τ)	The circadian period of active wakefulness, body temperature, and drinking behavior are significantly shortened in old rats	79
	Relationship between circadian period and wake time, circadian phase, and diurnal preference in older subjects are not different from those in young subjects. Period did not change with age in two inbred strain of mice	38, 75, 78, 111, 113
	Circadian period is significantly lengthened in two inbred strains of mice and in blind humans	37, 74, 80, 114
Phase of entrainment	Delay in evening activity peak and advance in morning activity peak. Age-related difference in the phase of entrainment of activity rhythm is greater under LD 6:18 than LD 14:10. Age-related alterations in the phase of entrainment to LD cycle	2, 3, 36, 37, 88, 96, 103, 115, 116, 117, 231
	Relationship between circadian period and wake time, circadian phase, and diurnal preference in older subjects are not different from those in young subjects	113
Attention pattern rhythm	Age modifies rhythm in attention and also the distribution of interindividual differences which occur in kindergarten children	117
Phase-resetting	Phase shifts do not differ among old and young groups. Compared to the young, older adults are significantly phase-advanced in sleep, cortisol, and aMT6s onset, but not in aMT6s or temperature rhythm. The effect of increase in daily light duration is attenuated in old animals compared to younger lemurs. Age-related increase in light-induced phase shifts. Loss of responsiveness to phase shifting/entraining effect of stimuli. Aging is associated with attenuation of 8-OH-DPAT-induced phase shift and its ability to attenuate the photic phase. Decreased sensitivity to phase delaying effect of light. Magnitude of phase delays does not differ between old and young individuals, but phase advances are significantly attenuated in old	2, 14, 66, 69, 96, 116, 118, 119, 120, 121, 122, 123, 124
Feeding rhythm	Age-related shift from nocturnal to diurnal eating habits in mice. Rhythm in ingestive responses to SKF-10,047 is absent in old animals. Also, old mice failed to show any significant increase in ingestive response following opiate administration	125, 126
Phase-shifting effects of nocturnal exercise	The dim-light melatonin onset (DLMO) phase delays more after exercise. On average, the difference in phase shift between exercise and control conditions is similar for old and young subjects	127

Table 1.1. (*cont.*)

Criteria	Comments	Reference(s)
Rest/activity rhythm	Amplitude of core body temperature (cBT) rhythm is reduced in elderly subjects	96, 102, 103, 107, 111
Respiratory rhythm	Aging decreases the amplitude of circadian respiratory rhythm and modifies the phases of ultradian respiratory rhythms	127
Body temperature rhythm (cBT)	Rest/activity rhythm becomes fragmented in aged primates, and shows increased activity during resting period. Aging induces a decrease in amplitude of cBT rhythm and an increase in energy consumption. Various hormonal secretions decrease with age. Activity and CBT rhythms do not change simultaneously with age. In comparison to adults, CBT rhythm in the elderly is poorly developed. Daily activity episodes, total activity, and body temperature are significantly lower in old mice	25, 26, 47, 88, 106, 109, 128, 129, 130, 131
Melatonin rhythm	Plasma melatonin concentration during sleep is considerably decreased with aging in men	132
Myelopoietic progenitor cell rhythm	The d-8 CFU-S cell numbers decline in aging mice. The amplitudes and 24 h mean values decline in aged mice. With aging a significant advance of peak is observed	133, 134
Mitotic activity of endocrine cells	Old mice show higher mitotic indices during the darkness. The average mitotic activity over the entire cycle is lower in old mice	135
Rectal temperature, organ weights, blood pressure, and Ca and Mg	17 parameters could be approximated in young rats, 1 parameter in old animals. In some cases large age-dependent alterations in amplitude could be observed	136
Blood pressure and heart rate during sleep	Sensitivity of baroreflex control of heart rate is significantly depressed; spontaneous increase in mean arterial pressure and body temperature during REM sleep and drop at the end of REM sleep are significantly enhanced in aged rats	137
Food anticipatory activity rhythm to restricted feeding	Under restricted feeding, aged rats take longer to show food anticipation pattern and show a lower amplitude food anticipation rhythm compared to young rats. Despite the absence of entrainment to LD cycles, both SCN-lesioned and aged groups show entrainment to restricted feeding	138, 139, 232
Activity rhythm	Age-related disruption of circadian timing. Older mice showed decrease in amplitude and high levels of activity during the light phase of LD cycle. Activity rhythms of older animals "split"	140, 141
Shift work	Ability to do shift work decreases	142, 143, 144, 145, 146, 147, 148, 149
Clock genes		
Clock genes	Impairment of *mPer* expression	150
BMAL1 and PER	Molecular clock mechanism in the SCN, PVN, and pineal body is preserved against aging, whereas impairment of light-induced *Per1* induction in SCN results in impaired behavioral photic entrainment in aged rats	150
CLOCK	CLOCK mutant mice respond to low-dose irradiation by accelerating their aging program	150, 151, 233, 234
Per1	Old rats display age-related period shortening in *mPer1* rhythmicity	
Per2	Age-dependent difference in mice is found in the case of *mPer2* (but not *mPerl*) mRNA expression	153
Per3	Strength of association of 4-repeat allele of PER3 with evening types, and 5-repeat allele with in morning types attenuates with age	
Per1–2, CLOCK and Bmal1	Age alters the 24 h expression profile of *Clock* and its binding partner *Bmal1* in the hamster SCN. Light pulses induce smaller phase shifts in old animals than in young, leads to decreased induction of *mPer1*, but not of *mPer2* in the SCN of old hamsters	155
Per1–3, Bmal1	The evening *mPer* expression in the liver of old rats show significant decrease. The heart showed similar profiles with only a tendency towards a decrease of *mPer* expression and an increased *Bmal1* expression in the evening in old rats	156

Table 1.1. (*cont.*)

Criteria	Comments	Reference(s)
Per2 and Bmal1	A significant age-related difference in *mPer2* expression is detected	
Jun-B and Jun-D and CRH	In young rats, light induces a robust increase in the number of Jun-B positive cells in SCN. In middle-aged rats, the light-induced increase in the number of Jun-B positive cells was significantly attenuated. Transplantation of fetal SCN tissue into middle-aged rats successfully restored light-induced Jun-B expression to the levels of young rats. Unlike young rats, no rhythm in CRH mRNA expression is detected in the PVN of old rats	157, 158, 159
TAT	Age-related shift in the peak TAT enzyme activity rhythm	160
Role of Clock	Age-related changes in circadian rhythmicity occur equally in wild-type and heterozygous CLOCK mutant mice	161
Central and peripheral oscillators		
Glucose utilization	Unlike young animals, old rats show a more gradual increase in LCGU after lights-on, with no further increase prior to the LH surge, and a premature decrease during the afternoon and evening	18
Synaptic number	The population of the major SCN synapses formed with dendrite and total number of synapses reduce with advancing age	162
Morphology	The neurons and neuroglial cells in SCN of the old rats display more lipofuscin accumulation in comparison to younger animals. More neuroglial cells with broader somatic membrane appositional to that of neuron participate in satellitosis in the old age group	163
Electrophysiological properties	Aging leads to decrease in amplitude of impulse activity in dispersed SCN neurons in cultures. The frequency of spontaneous inhibitory post-synaptic currents is reduced in SCN of older animals	19, 163, 164, 165, 166
Responsiveness to melatonin	In SCN slices from aged mice, PACAP alone induced comparable levels of phospho-CREB	167
VIP mRNA expression	Aging selectively decreased the VIP mRNA expression in SCN without affecting AVP mRNA or SS mRNA	51
V1a and V1b receptors	The amplitude of V(1a) receptor mRNA rhythm is reduced and of V(1b) mRNA elevated in aged group	168
VIP	Loss of day–night difference in VIP mRNA levels in the SCN of aged rats	50
VIP, VPAC2, and PAC1 receptors	Aging reduces VIP and VPAC2 receptor mRNA and eliminates diurnal expression of VIP mRNA within the SCN of aged male rats	169
Cytokine receptors	Marked changes of several functional, cellular, and molecular parameters are observed in the aged SCN	170
Presynaptic network including GABAergic terminals	The number of and the area covered by presynaptic terminals and by their GABAergic subset are significantly decreased in old mice. Marked reduction in synaptic network of aging SCN, which also affects GABAergic terminals. Alterations of the GABAergic network during senescence	171, 172
AVP	Circadian organization in rats is progressively disturbed in senescence. An increase in SCN volume and nucleus diameter and an overall decrease in cell density are observed. Staining with antivasopressin and morphometry revealed a decrease in the number of SCN neurons, while the vasopressin cells became larger	16
Fos expression	No effect of age on the pattern of *c-fos* induction by light in SCN	173
Light-induced gene expression	A decrease in the response of *c-fos* and NGFI-A but not NGFI-B is noticed in the SCN of old animals after photic stimulation	20, 155
Adrenoceptors	Alpha(1)ARs and betaARs density in heart and brain and betaARs in submandibular glands are significantly lower in old mice	174
Neurotransmitter binding	In the aged animals, time of the binding maxima is no longer locked to the same phase of the LD cycle. Cycle amplitudes are smallest in young animals, increases significantly in old rats	175

Table 1.1. (*cont.*)

Criteria	Comments	Reference(s)
Lipogenic enzymes, serum triglyceride and insulin levels	The activities of malic enzyme and alpha-glycerophosphate dehydrogenase are lower in the liver of old rats in contrast to young animals. Unlike young animals, the activity of glucose-6-phosphate dehydrogenase in old animals does not show any circadian rhythm	176
Norepinephrine level and serotonin	Old rats have lower amplitude and lower mesor values of 24 h variations in pineal NE content and 5-HT turnover	177
Melatonin and its receptor expression	Circadian rhythm of 2-[125I]iodo-melatonin binding showed age-related decrease in the SCN of old mice. Mel1a receptor mRNA expression in SCN decreased during day, but not during night	62a
Central and peripheral oscillators	While phase-resetting in the SCN following an advance or a delay of light cycle appears nearly normal in young rats, resynchronization of the liver is seriously disrupted. Arcuate nucleus and pineal gland exhibited faster resetting in aged rats relative to young controls. SCN rhythmicity in old rats displays age-related shortening in circadian period. Circadian rhythmicity in some peripheral tissues is unaffected by aging, while in other tissues is either phase advanced relative to the light cycle or absent	122, 153
Stress hormones and leptin	Aging augmented circulating leptin. Corticosterone levels correlated significantly with plasma adrenocorticotropin releasing hormone (ACTH) and leptin only in young rats	178
Lutenizing hormone (LH) and follicle stimulating hormone (FSH)	Baseline LH levels show a significant 24 h periodicity in adult males. FSH concentrations exhibit significant diurnal variations in juvenile and adult males. There is a significant influence of age on the temporal pattern and 24 h plasma hormone levels	179
Liver or brain enzymes	15 enzymes from young and 8 from aged mice showed a significant regression to a 24 h cosine curve. Old mice showed larger variance in 9 enzymes. 12 enzymes from aged mice had decreased mesors, 2 had increased mesors, and 9 were unchanged	180
Immune response, number of cells in lymphoid organs	With age, the peaks in amount of cells in thymus and its mass in the night and in autumn and peaks in the antibody titers in autumn diminish and intrasystemic relations undergo changes	181
HCRT-1 levels and HCRT receptors	Old rats had significantly less HCRT-1 in the CSF and continued to have low levels of HCRT-1 after 8 h of prolonged waking	182
Sensitivity of AD receptors	Old rats have more extracellular levels of AD and sleep compared to young rats across the 24 h diurnal cycle	183
5-HT7 receptors	Aging significantly inhibited the phase advances in running-wheel rhythms induced by 8-OH-DPAT	184
D2 receptor binding	Younger human subjects show reduced evening D2 receptor binding while older subjects show increased D2 receptor binding	185
2-[125I]iodo-melatonin binding	Specific 2-[125I]iodomelatonin binding sites are seen in the SCN of prenatal hamsters but not in older hamsters	186
Calbindin D28K protein cells	Calbindin expression in the SCN is modified by aging. Amplitude of oscillation in calbindin expression is damped, with a lower immunointensity during daytime and delayed decrease during night	187
Effect of lithium	The basal levels of phosphorylated GSK-3 (pGSK-3) protein expression in old hamsters are much lower, and lithium did not affect the period of the activity rhythm or pGSK-3 expression	188
Bcl-2 and Bax expression	In old rats CORT exposure decreases the bcl-2 to bax mRNA ratio in the morning but not in the evening	189

Table 1.1. (*cont.*)

Criteria	Comments	Reference(s)
LH, FSH, testosterone, inhibin B	Inhibin B and FSH levels are generally lower in old monkeys, but neither inhibin B nor FSH showed circadian rhythms	
GH, PRL, ACTH, and cortisol	Circadian profile of plasma melatonin in old subjects is flattened. A lowering of PRL and GH circadian profiles is also seen with aging	46
Cortisol and DHEAS	The circadian profile of serum cortisol is flattened in elderly subjects, with higher cortisol levels at night. The decline of DHEAS secretory pattern is age related. Cortisol/DHEAS molar ratio progressively increases with aging	190
GH and cortisol	Increasing age is associated with a decline in GH secretion and an elevation of evening cortisol levels	191
Endocrine rhythms	Peripheral levels of cortisol, melatonin, thyroid stimulating hormone, testosterone, prolactin, and GH decreases with age, but overall cortisol secretion increases	192, 193
Pineal		
Effect of melatonin and pineal grafting	Pineal grafted from young donors into the thymus of old syngeneic male mice resulted in an increase in survival	194
Pineal grafting	Pineal grafted aged mice display a remarkable maintenance of thymic structure and cellularity and preservation of T-cell-mediated function, as measured by response to oxazolone	195
Clock genes in pineal	Expression of clock genes and its associated proteins is impacted by aging. Age-related difference in *mPer2* expression is detected	151, 156
Melatonin/agonist corrects age-related changes	Old hamsters on control diet show little or no phase shifts in response to a dark pulse. Old hamsters fed with S-20098 show phase shifts significantly greater than those in old controls	69
Pinealocytes	The number of pinealocytes per unit surface of aged rats decreases	196
Pinealocytes and other innervations	Pinealocyte number in old animals is decreased. Sympathetic innervation of the gland is drastically reduced in older animals	197
Neuroaxonal dystrophy (NAD)	Loss of nerve terminals and development of NAD in older rats. Age-related loss of normal noradrenergic innervation and development of NAD. Pineal NGF content is increased in aged rats	198
Melatonin	With aging, plasma melatonin concentration during sleep is considerably decreased in men	132, 152, 199
NAT	In old hamsters nocturnal rise in melatonin is absent	23, 24
Serotonin (5HT)	Administration of L-tryptophan increased 5-HT synthesis in old animals in a time-independent manner	200
Hypothalamic–pituitary–adrenal (HPA) axis	Aging is accompanied by impairment of hypothalamic–pituitary–adrenal system. Corticosterone level shows a distinct age-related circadian pattern. Basal levels of DOPA, DHPG, MHPG, DA, DOPAC, HVA, NE, and EPI are higher in old rats. Selective impairment of nocturnal melatonin and serum cortisol levels has been observed in elderly subjects. Amplitude of cortisol rhythm and nocturnal cortisol increase are significantly reduced with age. The sensitivity of the hypothalamic–pituitary–adrenal axis to the steroid feedback is significantly impaired in old subjects. The serum DHEAS levels are significantly lower in elderly subjects. A significant increase of the cortisol/DHEAS molar ratio is evident in elderly subjects. The reactivity of the hypothalamic–pituitary–adrenal system during immobilization at 15.00 is lower and at 9.00 higher in old animals. Circadian variations in stress reactivity of glutathione reductase during aging are accompanied by similar changes in stress reactivity of the hypothalamic–pituitary–adrenal system. Circadian rhythm in stress responsiveness as measured by corticosteroids and glutathione reductase is attenuated in old animals and age-related changes in overall level of response to afternoon stress are also seen in corticosteroid and glutathione reductase	201, 202, 203, 204, 205, 206, 207, 208

Table 1.1. (*cont.*)

Criteria	Comments	Reference(s)
Interrelation between feeding, circadian rhythm	DHEAS and cortisol show pronounced diurnal plasma pattern, with peaks occurring in late morning, but only DHEAS show an age-related decline in primates	209, 210, 211, 212, 213
Central versus peripheral clocks	Aging affects rhythms in some but not all tissues and may act primarily on interactions among circadian oscillators, attenuating ability of SCN to drive damped oscillators in the periphery	122, 153, 156
Photoreceptor	A photoreceptor candidate for entrainment of non-visual photoreception remains in cone population in aged rd/rd mice. Aged rd/rd cl mice show substantial transneuronal retinal degeneration leaving only the ganglion cell layer and little of the inner nuclear layer. Negative masking increases with age while positive masking decreases in retinal degenerate mice. Older subjects have lower mean 24 h corneal hysteresis and corneal resistance. Timings of CCT and IOP rhythms are delayed by aging	173, 214, 215, 216
Sleep		
Difficulty in falling asleep or maintaining sleep, resulting in insufficient sleep, difficulty with concentration and memory, and overall decrease in quality of life. Age-related changes in the circadian modulation of sleep-spindle frequency during nap sleep. Age-related impairment of non-REM sleep at all circadian phases. Age-related decline of sleep-dependent consolidation		8, 9, 10, 11, 27, 53, 107, 108, 115, 116, 217, 218, 219, 220, 221, 222, 223, 224, 225, 226, 227, 228, 229, 230

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Possible mechanisms and consequences of age-related changes in the middle years of life

Julie Carrier

Introduction

The current overwhelming evidence that aging is associated with a significant increase in sleep–wake cycle complaints has important individual, social, and economic consequences. These age-related changes occur as early as the middle years of life, with over 35% of the population in their forties to sixties reporting sleep difficulties [1]. A number of factors – including health problems, medication side-effects, and specific sleep disorders – account for this age-related increase in sleep difficulties. However, critical changes in the sleep–wake cycle are also observed in "optimal aging," i.e. when there are no medical, psychiatric or specific sleep disorders present. Importantly, the lifestyles of middle-aged subjects make them particularly at risk for the more serious consequences of sleep problems. Multiple social, family, and professional responsibilities limit potential behavioral strategies to alleviate sleep difficulties (e.g. no opportunities to nap or no flexibility to determine sleep schedules) and increase the number of situations that challenge sleep–wake cycles (shift work, jet lag, caring for children at night, etc.).

Changes in sleep organization in the middle years of life

Age-related changes in polysomnographic sleep parameters

Changes in sleep organization are a hallmark of the normal aging process (for one of our reviews, see [2]). Subjective sleep complaints multiply in the middle years of life, and almost all sleep parameters show significant age effects between the ages of 20 and 60 years [3, 4, 5, 6, 7]. We and other researchers have demonstrated that, compared to young people (20–39 years), healthy middle-aged subjects (40–60 years) have shorter, shallower sleep that is more fragmented with awakenings [4, 6]. Non-REM (NREM) sleep changes drastically with aging [5, 8]. Compared to young individuals, middle-aged individuals show a substantial reduction in slow wave sleep (SWS; stages 3 and 4) and a rise in percentage of lighter NREM sleep stages (stages 1 and 2). The effect of aging on REM sleep is more controversial. Some studies have reported a reduction in REM sleep latency, less REM sleep during the night, and more REM sleep in the first part of the sleep episode whereas other studies have found no age-related changes on these parameters [4]. To illustrate the magnitude of age-related changes, Figure 2.1 presents polysomnographic sleep parameters in 47 healthy young (20–39 years; mean=23.3, s.d. = 2.4) and 39 middle-aged (40–60 years; mean 51.9, s.d. = 4.6) subjects with no sleep complaints or disorders (sleep apnea index <5 and periodic leg movements in sleep <10) (unpublished data). On average, middle-aged subjects showed almost no SWS, with reductions of about 30 minutes in sleep and 5% in sleep efficiency compared to young subjects.

Age-related changes in NREM sleep microstructure

Spectral analysis of NREM sleep EEG points to decreases in spectral power in delta (0.5–4.0 Hz), theta (4.0–8.0 Hz), and sigma (12–14 Hz) frequencies in subjects from their twenties to their sixties [5, 6]. Sleep spindles (waxing and waning 12–15 Hz rhythmic waves, lasting at least 0.5 second) [9] are an important characteristic of NREM sleep. Compared to young subjects, middle-aged individuals show lower number, density, and duration of sleep spindles [10]. Importantly, NREM sleep rhythms potentially play a role in protecting the sleeping brain from afferent stimulations and consolidating memory traces acquired during wakefulness (see below) [11].

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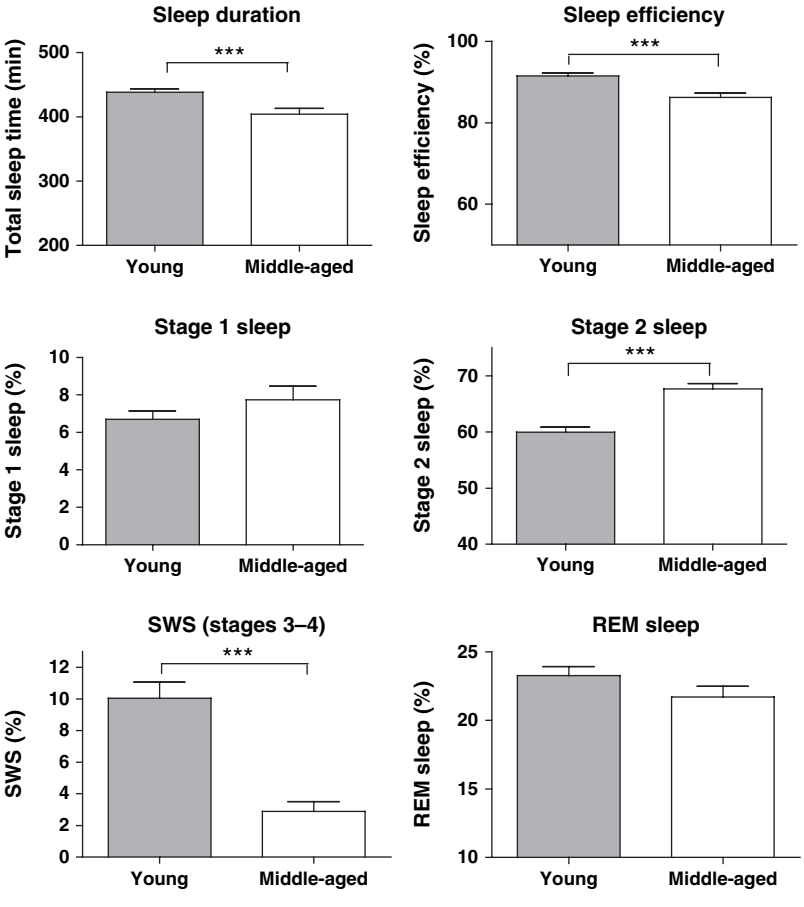

Figure 2.1. Sleep parameters in a sample of young (n = 47; 20–39 years) and middle-aged subjects (n = 39; 40–60 years). Subjects reported no sleep complaints and had no significant medical or psychiatric conditions. They were free of all medication that could affect the sleep–wake cycle. Peri-menopausal women and women using hormonal contraceptives or receiving hormonal replacement therapy were excluded. Pre-menopausal women were studied during the follicular phase of the menstrual cycle. Student's t-test showed that, compared to young subjects, middle-aged subjects showed shorter sleep duration ($p < 0.001$), lower sleep efficiency ($p < 0.001$), lower % of SWS ($p < 0.001$) and higher % of stage 2. In this sample, no significant effect of age was found on % of stages 1 and REM.

Age effects on NREM sleep EEG differ between brain to pographical sites [7] in parallel with age-related changes in gray matter density of the brain. Global cortical thinning is significantly apparent in subjects from their twenties to their sixties [12] and cortex atrophy seems to be especially marked in the frontal lobes [12, 13, 14]. Figure 2.2 presents the spectral power of frequency bins in young and middle-aged subjects, showing a modulation of age effects between cerebral sites (same sample as in Figure 2.1; unpublished data). Between 2 and 6 Hz, the effect of age on NREM sleep spectral power is more prominent in anterior brain areas (Fp1 and F3), while it is more prominent in Fp1, F3, and O1 between 7 and 21 Hz. We also measured the topography of age-related changes in spindle density in young and middle-aged subjects (see Figure 2.3). Compared to young subjects, middle-aged subjects showed lower spindle density (number of spindles per minute of NREM), and this effect was more prominent in frontal brain areas than in more posterior derivations.

Gender differences in sleep in middle age

It is not clear when in the aging process gender differences in polysomnographic sleep appear in healthy subjects. Gender differences in quantitative sleep EEG measures have been reported in subjects as young as 20–29 years of age [15], with young women showing higher slow wave activity than young men. In subjects between the ages of 20 and 60 years, we found differences between men and women in a few parameters [4]. Women spent more time in bed than men, as indicated in their sleep diaries. In the laboratory, women showed more SWS, fewer awakenings, and shorter REM latency. Importantly, there was no significant interaction between age and gender for any of the sleep parameters, which suggests no difference in the influence of aging between men and women. We also assessed the effects of age and gender on sleep EEG power spectral density in a group of 110 men and women aged 20–60 years [5]. Women showed higher spectral power than men in delta, theta, low alpha,

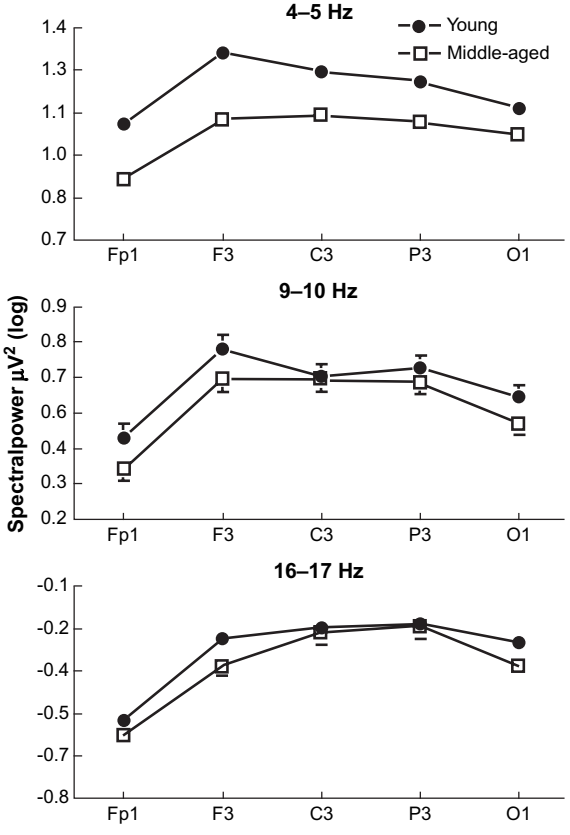

Figure 2.2. All-night NREM sleep spectral power for some frequency bins (4–5 Hz, 9–10 Hz, 16–17 Hz) showing a significant interaction between age and derivation ($p > 0.05$) in three-way ANOVAs (Age group, Gender, and Derivations). Spectral analysis was computed per 1-Hz bin between 1.00 and 32.00 Hz on the left derivations (same subject sample as in Figure 2.1). Middle-aged subjects showed lower power in delta/theta (2–6 Hz) than young subjects, and this difference was more prominent in anterior derivations. Middle-aged subjects showed lower power than young subjects in theta/alpha (7–13 Hz) and low beta (14–21 Hz) frequencies, and these differences were more prominent in anterior and occipital brain areas.

and high sigma frequency bins (0.25–9.00 Hz, 14.25–16.00 Hz). These differences were constant across the night. Again, no significant interactions emerged between age and gender, suggesting that age-related changes in NREM sleep EEG were similar in men and women.

We know that sleep and quantitative sleep EEG vary with the level of reproductive hormones across the menstrual cycle [16], during pregnancy [17], and when using hormonal contraceptives [18], or hormone replacement therapy [19]. Almost no studies to date have carefully controlled for these influences when determining whether the sleep–wake cycles of men and women age at a different rate. Further research is needed to understand the influence of hormonal status between the genders and its interaction with the aging process.

Periodic leg movements in sleep (PLMS) in middle-aged subjects

The prevalence of some primary sleep disorders such as sleep apnea disorder (pauses in breathing during sleep) and restless sleep syndrome (overwhelming urge to move the legs usually caused by uncomfortable or unpleasant sensations in the legs) starts to increase significantly in the middle years of life and undoubtedly affects sleep considerably. Periodic leg movements in sleep (PLMS) are stereotyped, repetitive movements of the legs during sleep. These movements last 0.5–5 seconds and occur at intervals of approximately 20–40 seconds. A PLMS index (PLMSI: number of movements per hour of sleep) greater than 5 is considered abnormal. It is now well established that PLMSI prominently increases with age in both patient and non-clinical populations [20, 21, 22]. However, it still is unclear if PLMSI greater than 5 should be considered a pathological condition in middle age. In a study on 70 healthy middle-aged subjects (40–60 years) without sleep complaints, we investigated whether the PLMS index is related to sleep quality in older subjects without sleep complaints [23]. We found that a large proportion of middle-aged subjects without sleep

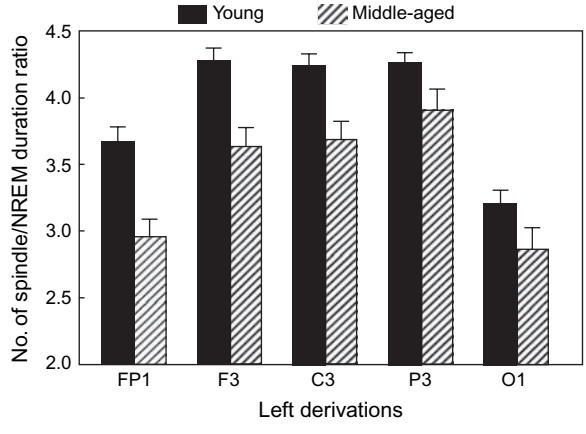

Figure 2.3. Number of spindles per minute of NREM sleep for left derivations (same subject sample as in Figure 2.1) The ANOVA showed a significant interaction between age and derivation ($p < 0.01$). Contrast analyses revealed significant age-related differences for all derivations ($p < 0.03$), except for the O1 derivation ($p = 0.07$).

complaints show a PLMSI higher than 5 (55% of men and 28% of women). However, PLMSI had no influence on polysomnographic sleep quality in this sample. These results cast doubt on the relevance of PLMSI as a pathological index for middle-aged subjects without sleep complaints, and support the notion that an increase in PLMSI may be part of the normal aging process associated with loss of dopaminergic function.

Age-related sensitivity to sleep–wake cycle challenges

Importantly, middle-aged people show not only sleep changes under habitual conditions, but they also show more sensitivity to challenges to the sleep–wake cycle. For example, middle-aged people report more problems adjusting to shift work than younger individuals [24]. They also adapt more slowly to jet lag [25], and their sleep is more sensitive to stress hormonal factors [26].

Given the age-related increase in complaints related to jet lag and shift work, sleep in older subjects may be particularly vulnerable to circadian phases of high wake propensity, which means it would be more difficult for older people to sleep at the "wrong" circadian phase (i.e. in the daytime) [27]. We evaluated the ability of middle-aged subjects to sleep during the day after a sleep deprivation. Young and middle-aged subjects were sleep-deprived for 25 hours and recovery sleep was initiated in the morning, a time when circadian wake propensity normally increases (see below) [28]. Despite the sleep deprivation, both young and middle-aged subjects showed more wakefulness during daytime recovery than during a baseline sleep episode, due to the wake signal from the circadian timing system. However, compared to young subjects, middle-aged subjects showed greater wakefulness (decreased sleep efficiency) during daytime sleep versus night sleep (see Figure 2.4a). Importantly, the steeper increase of wakefulness in middle-aged subjects was observed after the first few hours (see Figure 2.4b).

Age-related changes in homeostatic and circadian sleep–wake regulation mechanisms?

A precise interaction between the homeostatic and circadian processes is required for optimal sleep and vigilance. The homeostatic process is a regulating mechanism whereby sleep pressure accumulates with time awake and dissipates during a sleep episode. The homeostatic drive for sleep has been studied in many species, from fruit flies [29] to various mammals [30, 31]. In humans, the intensity and dynamics of SWS and SWA (slow wave activity; spectral power between 0.5 and 4.5 Hz) reflect the time course of the homeostatic process (i.e. more time awake produces higher levels of SWS/SWA, whereas more time asleep is associated with lower levels of SWS/SWA). Using different wake duration intervals prior to a sleep episode, it was established that SWA increases with accumulated hours of wakefulness prior to sleep, according to a saturating exponential function [32, 33]. Results from recent studies show brain regional differences in homeostatic sleep regulation. First, SWA is more prominent in frontal-central brain areas compared to posterior regions [34, 35]. Furthermore, increase in SWS/SWA after a sleep deprivation is larger in frontal than occipital regions [36, 37, 38]. Thus, frontal brain regions seem to have a higher "recovery need" than more posterior areas.

The circadian process is the rhythmic pattern of sleep–wake propensity over 24 hours. A biological "clock" located in the suprachiasmatic nucleus controls the circadian process. In a normally entrained individual, circadian sleep propensity increases during the night and maximizes in the early morning hours, whereas circadian wake propensity increases during the day and maximizes in the evening [39, 40]. The circadian modulation of sleep–wake propensity can be felt in jet lag and shift work situations, where people try to sleep at times of high circadian wake propensity (which leads to fragmented sleep interrupted by wakefulness) and try to stay awake and productive at circadian times of high sleep propensity (which leads to low alertness). The combined action of the homeostatic and circadian processes maintains consolidated sleep episodes of about 8 hours during the night and about 16 hours of wakefulness during the day [41]. Aging may have a negative impact on the homeostatic and circadian processes, both individually and in interaction.

Age-related changes in homeostatic regulation

Alterations in the build-up function of the homeostatic process could explain decreasing SWS/SWA

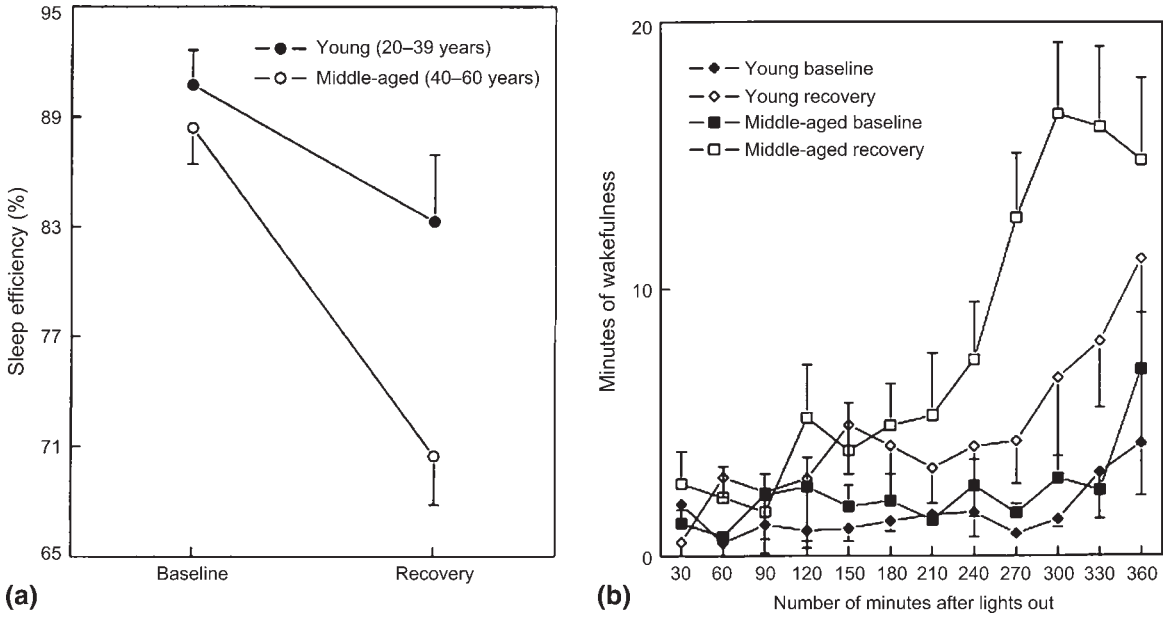

Figure 2.4. (a) Mean sleep efficiency (and SEM) in young and middle-aged subjects during baseline and daytime recovery sleep following 25-hour sleep deprivation [28]; (b) mean number of minutes of wakefulness per 30 minutes in young and middle-aged subjects during baseline and daytime recovery sleep [28].

with increasing age, especially in anterior areas of the brain. This would mean that the sleep (SWS/SWA) of older people is less sensitive to accumulated wakefulness. According to this hypothesis, similar increases in the number of waking hours preceding sleep would produce smaller SWS/SWA increases in older than in younger individuals. The impact of aging on the homeostatic regulation of SWS/SWA remains a matter of debate. Two separate animal studies have reported that aged animals exhibit reduced NREM sleep responses following sleep deprivation [42, 43]. Some studies in humans have reported that SWS enhancement following sleep deprivation tends to be less intense in older than younger subjects [28, 44, 45, 46]. The reduced ability of older subjects to increase sleep intensity following sleep deprivation seems particularly detectable in anterior derivations compared to more posterior brain areas [46, 47]. Nevertheless, some studies found no age-related differences in SWS/SWA rebound after sleep deprivation [48, 49], or found similar responses of young and older subjects to a reduction in homeostatic pressure (i.e. a nap) before the main sleep episode [50]. Importantly, even in studies showing similar SWS/SWA responses between younger and older subjects, SWS/SWA levels are always lower in older than younger subjects, regardless of the nature of the homeostatic challenge.

Age-related changes in circadian regulation in middle age

There are numerous reports in the literature of age-related changes in the phase of circadian rhythms. Older people indicate that they are morning types more often than young people [51]. This difference starts during middle age [4]. Figure 2.5a presents the relationship between age and chronotype in subjects between 20 and 60 years old. Increasing age is associated with higher morningness. Research on habitual sleep–wake patterns in young and middle-aged subjects using sleep diaries corroborates this age-dependent tendency towards morningness [4]. Compared to young subjects, middle-aged subjects tend to go to sleep and wake up about one hour earlier. Studies that controlled for masking effects on physiological circadian rhythms have confirmed that, compared to younger subjects, middle-aged subjects show a phase advance in temperature and melatonin circadian rhythms associated with earlier sleep timing [52, 53]. Figure 2.5b and c presents temperature and salivary melatonin circadian rhythms in young and middle-aged subjects. On average, habitual bedtime, habitual wake time, minimum circadian temperature rhythm, and melatonin rhythm onset all occur one to two hours earlier in middle-aged subjects. These age differences are similar

to those reported in healthy elderly subjects. A recent study found a similar acrophase (fitted peak time) for the salivary melatonin circadian rhythm in both young and middle-aged subjects [54]. However, saliva samples in that particular study were collected in the subjects' natural environment, where the masking effects of light and posture changes may have compromised the accuracy of melatonin circadian phase estimates.

Age-related increase in wakefulness during sleep may be associated with a phase angle change between the signal from the circadian clock and sleep–wake cycles. According to this hypothesis, the advance of the circadian signal would be larger than the advance of the sleep–wake cycle. As a result, the increase in the circadian wake signal would occur too early during the sleep episode, leading to more awakenings during sleep in older than younger individuals [55]. This interpretation has led to the suggestion that changing the phase position of circadian rhythms (via bright light exposure, for example) might alleviate sleep complaints in older subjects [56]. It has also been suggested that age-dependent reductions in amplitude of the sleep–wake cycle (more sleep during the day and more wakefulness at night) is linked to age-dependent attenuation of the output signal from the circadian pacemaker. According to this view, there would be an age-dependent attenuation in the ability of the circadian pacemaker to create the correct internal temporal environment for restful sleep at night and alert wakefulness during the day. Importantly, young and middle-aged subjects show similar amplitudes of temperature, melatonin, and vigilance circadian rhythms, as well as similar phase angles between the sleep–wake cycle and physiological circadian rhythms (see, e.g. Figure 2.5b and c) [52, 53, 57]. In conclusion, the phase advance hypothesis predicts earlier bedtimes and wake times in middle-aged compared to young individuals. However, circadian hypotheses concerning phase angle or amplitude cannot explain the age-related increase in wakefulness during sleep. A different explanation is required.

The mechanisms that underlie age-related advance of the biological clock signal have yet to be determined. Based on the phase-response curve to light exposure [58, 59], one explanation is that older individuals might be exposed to more light in the morning, which would constitute a daily phase advancing stimulus. In a recent study, we sought to determine whether the phase advance of circadian melatonin rhythm in middle age was related to different patterns of habitual light exposure [53]. We observed that both young and middle-aged subjects were exposed to bright light (1000 lux and more) for approximately 1.5 hours per day. Figure 2.5d presents the mean number of minutes spent in different light exposures (0–100 lux, 100–500 lux, 500–1000 lux, and 1000 lux and more) in young and middle-aged subjects. No effect of age group was detected on any light intensity range. Figure 2.5e shows the relative light exposure patterns (percentage of mean light exposure received) in young and middle-aged participants according to clock time. Middle-aged subjects showed lower percentages of light exposure during late evening/night and higher percentages of light exposure in the morning. Earlier habitual wake times explained the earlier light exposure patterns of older subjects. As illustrated in Figure 2.5f, when habitual relative light exposure was expressed relative to habitual bedtime, the differences between age groups disappeared. In other words, older subjects exhibit the same phase relationship as younger subjects between habitual relative light exposure and the sleep–wake cycle. Our results support the notion that differing habitual light exposure patterns are insufficient to explain age-related circadian changes in middle age. The mechanisms underlying the age-related phase advance of circadian rhythms are still unknown.

Desynchronization of the brain: vulnerability to sleep–wake cycle challenges with aging

The cerebral mechanisms underlying age-related sleep changes are unknown. We propose that aging is associated with changes in the processes regulating NREM sleep rhythms. As noted above, NREM sleep rhythms (delta and spindles) are among the most significant age-related sleep changes. As reviewed by Steriade [60] and demonstrated in several animal electrophysiological studies conducted by Steriade and others, some of the principal neuronal networks involved in NREM brain rhythms are: (1) corticothalamic (CT) neurons; (2) the recurrent inhibitory circuit between thalamic reticular (RE) and thalamocortical (TC) neurons; and (3) brainstem cholinergic projections to the thalamus (to both RE and TC neurons). This TCT dialogue produces complex wave sequences known as NREM sleep rhythms [11]. Importantly, NREM sleep rhythms are associated

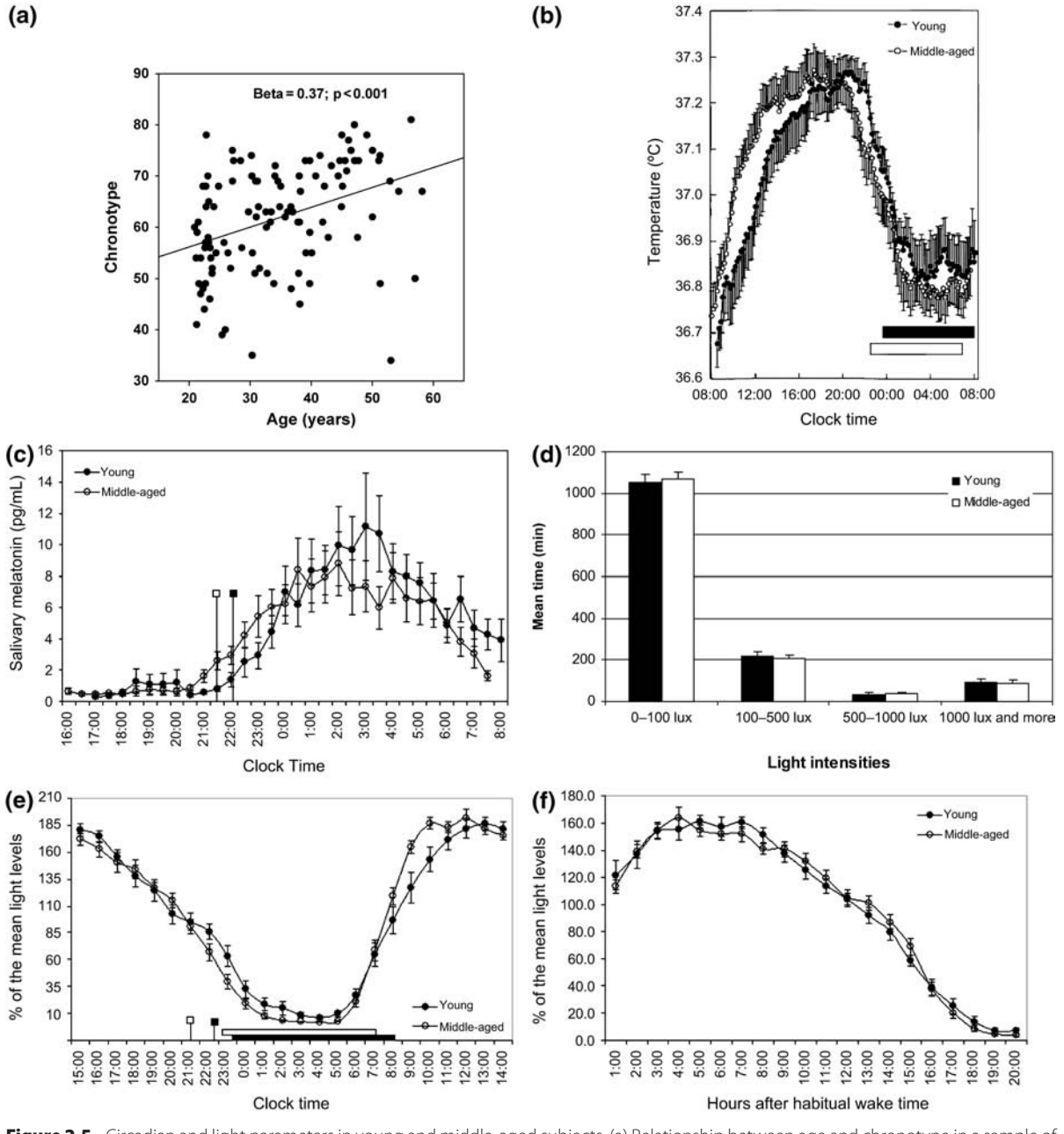

Figure 2.5. Circadian and light parameters in young and middle-aged subjects. (a) Relationship between age and chronotype in a sample of 110 subjects 20–60 years. Increasing age associated with higher morningness (i.e. earlier behavior). Data derived from [4]. (b) Ten-minute means (and SEM) of body temperature recorded during 25 hours in constant conditions for young (black circles; $n = 11$) and middle-aged (white circles; $n = 16$) subjects. Rectangles represent mean usual sleep periods for young (black rectangle) and middle-aged (white rectangle) subjects [52]. (c) Half-hour salivary melatonin concentration (mean and SEM) in young (black circles; $n = 16$) and middle-aged (white circles; $n = 21$) subjects during a 25-hour constant routine. Squares represent salivary melatonin onset (DLMO) in young (black square) and middle-aged (white square) subjects [53]. (d) Time in minutes (and SEM) spent in different light intensities for young and middle-aged subjects (same sample as c and d) [53]. (e) Habitual light exposure patterns in relative values (means and SEMs) for young (black circles; $n = 15$) and middle-aged (white circles; $n = 18$) subjects. Rectangles indicate the timing of the habitual sleep episode for young (black rectangle) and middle-aged (white rectangle) subjects. Squares represent salivary DLMO for young (black square) and middle-aged (white square) subjects. Time point 01:00 hours indicates averaged relative light received during the 1st hour following habitual wake time. (f) Habitual light exposure patterns in relative values adjusted to habitual wake time (means and SEM) for young (black circles; $n = 15$) and middle-aged (white circles; $n = 18$) subjects. Time point 01:00 indicates averaged relative light received during the first hour following habitual wake time [53].

with prolonged TC and cortical neuron hyperpolarizations that inhibit afferent signal transmission to the brain [11]. NREM sleep oscillations are therefore believed to protect the sleeping brain from stimulation [60]. Age-related changes in the mechanisms underlying NREM sleep oscillations may explain not only changes in sleep parameters but also the greater difficulty that older subjects have maintaining sleep, especially under challenges.

For example, the reason for the decreased ability of middle-aged subjects to sleep in the daytime remains unknown, and cannot be explained solely by malfunction of the circadian timing system. If that were the case, the fact that the sleep of older subjects is more sensitive to "unfavorable" circadian phases would suggest that the circadian wake signal gets stronger as we get older. However, results from human and animal research do not support this hypothesis. Instead, studies have found no change or even a reduction in the amplitude of many circadian markers in older subjects (melatonin, temperature, cortisol) [52, 61, 62, 63]. We propose that the amount of SWS/SWA (i.e. brain synchronization) is critical to "override" the circadian waking signal [28, 64]. According to this hypothesis, the daytime circadian signal is more likely to disturb sleep, since the amount of SWA/SWS during daytime recovery sleep is low. Thus, the decreased SWS/SWA associated with aging amplifies sleep disturbances caused by the daytime circadian waking signal [28]. This interpretation is supported by the observation that the firing rate of the suprachiasmatic nucleus (SCN) increases during SWS deprivation in rats [65], while it decreases during recovery sleep after sleep deprivation, when SWA is high [66]. Overall, these results suggest that sleep synchronization decreases the circadian signal's impact on sleep.

The importance of exploring the effects of age-related changes in middle age: brain synchronization and plasticity

Age-related changes in the neural correlates of NREM sleep oscillations may also underlie changes in memory and brain plasticity. Sleep is associated with cognitive functions and brain plasticity in several ways. Our research group and others have demonstrated that delta waves and spindles increase during sleep after procedural or declarative learning [67, 68, 69, 70]. A few studies have evaluated age-related changes in sleep-dependent consolidation, suggesting that sleep is less "efficient" for memory consolidation in older subjects [71]. Interestingly, recent results have also demonstrated that sleep (especially spindles) predict performance on general cognitive tasks such as the Raven's advanced progressive and non-verbal intellectual quotients [70, 72]. Although cognitive functioning has been associated with sleep quality in older subjects [73], only a few studies have evaluated the relationships between polysomnographic sleep parameters and cognition in older subjects. In these studies, better sleep quality (reduced sleep latency, less wakefulness during sleep, and higher SWA) was associated with better performance on various functions [74]. However, these studies did not assess the effects of age on these relationships.

Conclusions: what next?

Some key questions remain to be answered concerning the sleep–wake cycle in middle-aged subjects. First, we need to understand the cerebral mechanisms underlying age-related changes in the sleep–wake cycle. The design of effective preventive and therapeutic strategies for the middle-aged population depends greatly on our understanding of these mechanisms. Future research should identify vulnerability factors that put the older population more at risk for sleep–wake cycle disturbances (e.g. gender, menopause, stress, disease, etc.). Importantly, we must determine the consequences of age-dependent changes to the sleep–wake cycle in middle-aged individuals. It is known that sleep loss influences all aspects of life, including overall physical health, cognitive functioning, quality of life, psychological adjustment, metabolism, and hormonal regulation. Several recent studies have associated sleep problems with significant health consequences, such as higher risks of hypertension, diabetes, insulin resistance, obesity, depression, heart attack, and stroke [75, 76, 77]. Since middle-aged individuals are already more prone to many health conditions linked to sleep disorders, it is critical to elucidate how specific sleep changes (e.g. decrease in slow wave sleep) in middle-aged populations may put them more at risk for these conditions.

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Part 1
Chapter
3

Sleep and normal aging

Sleep throughout the menopausal transition and post-menopause

Theresa B. Young

Introduction

Sleep complaints are believed by many to be normal concomitants of menopause, but evidence in support of this association is not strong. Although several population surveys and large cohort studies designed to follow women through menopause have been ongoing for decades, several issues limit the ability to draw conclusions regarding any increased risk of sleep problems attributable to menopause from findings thus far. A major problem stems from the lack of primary focus on sleep disorders in most of the studies of midlife women. Most studies were designed to collect information on a wide range of hypothesized menopausal symptoms, lifestyle, well-being, and many other factors. With few exceptions, sleep disturbance has been only one of many factors being investigated and was usually assessed with a single question or check-list item, thus limiting the depth of findings regarding menopause and sleep. In addition, while major changes in the definition of menopause as a multistage transition have occurred recently, early studies viewed menopause as an abrupt change and categorized women as either pre- or post-menopausal. Furthermore, women's expectations of the impact of menopause on sleep, as well as the clinical approach to menopause, have changed over the past decade. These factors are likely to have various influences on the measured relationship of menopause and sleep, depending on the time period in which the data were collected. The analysis problem this creates is similar to having unmeasured confounding factors that add biases and "noise," making it difficult to obtain comparable, accurate estimates.

The goal of this chapter is to interpret previous study findings in light of limitations of the unique historical context and to provide a bridge to new perspectives emerging from ongoing cohort studies. The chapter will present factors relevant to assessing sleep problems in the menopausal transition that have changed over time, highlight conclusions from previous reviews of this topic, including a recent NIH State of Science Conference: Management of Menopause-Related Symptoms (NIH SOS: Menopause) [1, 2], focus on the findings of well-designed studies with population-based samples and appropriate methods of data collection and analysis, and explore future directions. In addition, newer ongoing cohort studies, with sleep in menopause as their specific aims, are described in Appendix 3. Detailed subjective and objective sleep data are being collected across well-defined menopausal stages in these cohorts, but findings are still preliminary. However, it is clear, even from the preliminary data, that new directions in thinking about menopausal effects on sleep and sleep disorders are emerging.

Challenges to understanding how sleep is affected by the menopausal transition: factors in flux

New definitions of the menopausal transition

The detailed physiology of the menopausal transition, a period of time driven primarily by hormonal changes resulting from the depletion of ovarian follicles, and how it may affect sleep have been elegantly described [3, 4, 5] and will not be reviewed in this chapter. Once believed to be an abrupt change, menopause is now seen as a transition over decades with distinct stages of hormonal fluctuations and menstrual cycle changes, with durations that vary individually. The World Health Organization, in 1996, developed a definition that included pre-, peri- and post-menopause [6]. By 2001, continuing interest culminated in the Stages of Reproductive Aging Workshop (STRAW) [3]. The consensus group developed a precise, comprehensive classification scheme, with the last menstrual period as stage 0, two stages of the menopausal transition before (−2, −1), and two post-menopausal stages (+1, +2) after. The precision allows better quantification of

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menopausal status for studies of potentially stage-dependent symptoms, such as sleep disturbance. This contrasts sharply with the simple dichotomy of pre- or post-menopause (yes, no), used in the earlier studies.

Changes in expectations of sleep problems and disorders during menopause

Expectations regarding menopause have changed over time, particularly since the advent of hormone replacement therapy (HRT) [4, 7]. A woman who is beginning the menopausal transition today is exposed to vastly different psychosocial cues than was a woman of just a few years ago. Striking changes in societal views of aging have occurred, and information (of varying accuracy) in the media, on the Internet, in pharmaceutical advertisements, and advice from health-care providers on menopause have shaped individual expectations of what menopause represents and what symptoms will be like. Recently, media reports of the sleep horrors of menopause have been abundant in magazines. Information and beliefs are then filtered and modified through societal groups. In addition to changes relevant to expectations of menopause over time (period effects), it is likely that expectations vary by ethnicity and socioeconomic status [8, 9].

Changes in clinical attitudes regarding menopause and sleep

Perhaps of greatest influence has been the "medicalization of menopause" [10, 11, 12, 13, 14]. The concept of medicalization, whereby a condition once considered normal suddenly requires medical intervention, began about 50 years ago and was fueled by the availability of hormone replacement therapy (HRT). The tendency to consider menopause a medical issue reached a peak in the HRT era of the 1980–90s. The great interest in HRT is reflected in the funding of several very large randomized trials, including the Women's Health Initiative designed to quantify the benefits and risks of HRT use [15]. By 2002, data from the trials failed to show a positive benefits to risk ratio [7]. The findings were highly publicized and led to a dramatic drop in popularity and use of HRT. Thus, over the past several decades, women have been exposed to the belief that menopause was a normal change and inevitable part of life, then to the medical model of menopause as a deficiency disease that, without therapy, causes a multitude of problems, including osteoporosis, sleep disruption, and other conditions and now to a search for a new paradigm.

With the heated controversy over adverse effects of HRT and search for herbal or other therapeutic alternatives, women face a dilemma with expectations of dreaded symptoms, and widely differing opinions of what to do, or to whom to turn. The underlying belief that a condition is normal versus abnormal surely influences a woman's assessment of her satisfaction with sleep and health. And, it may cause a spurious link of menopause to underlying, pre-existing sleep disorders and problems. Thus, many factors, including time period, family structure and social support, and greater expectations of living healthier lives, influence data on self-reported sleep habits and problems. In order to address the menopause–sleep association with current relevancy, it is vital that available findings on menopause and sleep be considered in the context of the history of how menopause has been defined, and the many influences on a woman's self-report of sleep problems and other symptoms.

Sleep problems in the menopausal transition: highlights and conclusions from reviews of population-based research

Increasing interest in reproductive aging and the advent of women's health as a specialty has led to a great deal of research on the menopausal transition. But, as mentioned, sleep disruption is only one of many symptoms or outcomes of interest. Consequently, most of the studies referred to in this chapter have used single-item sleep questions (e.g. do you have problems with your sleep? Yes or no). Given that past study findings are based on questions that generally lack specificity, and were subject to strong and ever-changing influences on self-assessed sleep, it is not surprising that results lack consistency and are difficult to summarize. Results of selected studies with adequate methodology to address sleep problems in menopause, and those rated good quality by the NIH SOS: Menopause panel [1], with emphasis on those with longitudinal data, are described in the following section and displayed in Table 3.1, which summarizes prevalence of sleep problems by menopausal stage, in Table 3.2, which gives findings of associations of sleep problems and menopausal stages, and in Table 3.3, which describes two studies with polysomnographic data on objective sleep quality. Baseline analyses and

some preliminary findings from ongoing cohort studies with special emphasis on sleep (described in detail in Appendix 3) are included in the tables and discussed in later sections.

Several reviews have collectively summarized over 50 cross-sectional and longitudinal studies of general population samples to compare sleep disturbance in pre-, peri-, and post-menopausal women. Although the trends support a higher prevalence of sleep disturbance across the menopausal transition, the point estimates vary widely by study, year of data collection, and country. For example, in a paper published in 1969 [16], 20%, 30%, and 40% of pre-, peri- and post-menopausal women, respectively, in the Netherlands reported a sleep problem. In a 1993 study of women in Great Britain, the figures were 40%, 50%, and 63% for pre-, peri- and post-menopause, respectively [17]. Data on women in the USA, collected in 1995–97 [18], showed prevalence of sleep problems of 31%, 41%, 44%, and 40% for pre-, early peri-, late peri-, and post-menopausal women, respectively. Thus, while there is a trend in the individual studies that implicates peri- and post-menopause as periods of more sleep disturbance, the ranges are overlapping and absolute differences between studies are large. It is possible that there has been an increase in sleep disturbances in women across all menopausal status categories, but that the rank order of increasing prevalence of sleep problems among pre-, peri-, and post-menopausal women prevails. Furthermore, the study findings may reflect cultural or time period effects.

In the first review of sleep in menopause, published in 1998, Krystal *et al.* [18] contrasted findings on sleep in peri- and post-menopause to sleep in pre-menopause. The authors noted their surprise in the lack of literature specific to sleep in menopause. They concluded that, in spite of findings suggesting that insomnia was directly related to the peri/post-menopausal period, definitive evidence was lacking. In a more recent review published in 2003 [19], Moline and colleagues noted that little had changed since the

Table 3.1. Prevalence of sleep problems by menopausal status

			Prevalence (%) of women with sleep problems in:			
				Menopause		
Study (ref)	Sample	Sleep measure	Pre-menopause	Early peri-	Late peri-	Post-
SWAN [8]	Baseline survey sample of multi-site community study, ages 40–55 years, N = 2 603	Survey question at baseline: "Experienced difficulty sleeping over the past 2 weeks?" (Yes)	31.4	39.6	45.5	43.2
Melbourne Women's Midlife Health Project [24]	Community sample, 1991–1998, N = 172, women with status change over 7 years	Checklist item measured yearly: "Trouble sleeping in last 2 weeks" (yes) Tabulated daily diary entries, ≥2nights/ month with difficulties	31	32	38	38–45
Sleep in Wisconsin Midlife Women*	Community sample (Wisconsin Sleep Cohort Study [26]), 1997–2008, N = 262, with 14 939 woman-months	1. Sleep onset	9.6	16.5	12.4	22.9
		2. Waking during night repeatedly	20.5	29.6	24.85	34.7
		3. Restless sleep	35.0	29.6	26.3	37.2
NIH SOS: Evidence report [2] estimates from reviewed studies	Summary of 8 cross-sectional and baseline cohort, studies conducted 1969–2003	All were single item: "difficulty with sleep" (yes/no)	16–42	39–47	Not given	35–60

*Preliminary data from T. Young.

Table 3.2. Associations of sleep problems and menopausal status

Study (ref)	Sample	Measure	Categories of menopausal status in models	Estimates
SWAN [8]	Community sample, 1995–1997, N = 2603, ages 40–55 years baseline sample	Odds ratios (95% CI) for having "difficulty sleeping in last 2 weeks," adjusted for age, BMI, health conditions, sociodemographic variables	1. Total sample:	
			Pre	Reference
			Early peri	1.11 (0.99,1.24)
			Late peri	1.33 (1.07,1.65)
			Post	
			Natural	1.21 (1.03,1.43)
			Surgical	1.55 (1.25–1.92)
			With HRT	1.12 (1.05–1.31)
			2. Without hot flashes:	
			Pre	Reference
			Early peri	1.10 (0.96,1.26)
			Late peri	1.40 (1.01,1.58)
			Post	
			Natural	1.26 (1.03,1.43)
			Surgical	1.19 (0.87–1.62)
			With HRT	1.03 (0.03–1.27)
Wisconsin Sleep Cohort Study [26]	1998–2000	Odds ratios (95% CI) for symptoms "often or always," adjusted for age, BMI		
		1. Waking repeatedly	Pre	Reference
			Peri	0.59 (0.25,1.43)
			Post	1.58 (0.70,3.54)
		2. Difficulty falling asleep		
			Pre	Reference
			Peri	4.18 (1.37,12.8)
			Post	2.77 (0.79,9.72)
		3. Waking repeatedly		
			Pre	Reference
			Peri	1.93 (0.7,5.36)
			post	1.57 (0.54,4.52)
		4. Dissatisfied with sleep		
			Pre	Reference
			Peri	2.01 (1.14,3.54)
			Post	2.23 (01.24, 4.01)
Australian Longitudinal Study on Women's Health [24]	Community sample, N = 8623, ages 45–50 years, surveyed in 1996 and 1998	Odds ratios (95% CI) for difficulty sleeping based on change in menopausal category, adjusted for confounding factors	From 1996 to 1998:	
			Remained pre-menopausal	Reference
			pre-peri	1.3 (1.1–1.5)
			peri-peri	1.4 (1.2,1.7)
			pre/peri-post	1.5 (1.2,1.8)
			post-post	1.2 (0.9,1.6)
			HRT users	1.5 (1.5,1.7)

Table 3.3. Sleep parameters measured objectively across the menopausal transition

Study	Polysomnography variable	Menopausal stage			
Wisconsin Sleep Cohort Study [27]		Pre-menopause (N = 496)	Peri-menopause (N = 116)	Post-menopause – with HRT (N = 189)	Post-menopause – no HRT (N = 226)
	Sleep stages, % (95% CI):				
	Stage 1	8.9 (8.2,9.5)	7.6 (6.9,8.4)*	9.2 (8.2,10)	8.1 (7.3,8.9)*
	Stage 2	59.9 (58,61)	59.4 (57,60)	56.4 (55,58)*	55.9 (54,58)*
	Stage 3–4	12.9 (12,14)	16.0 (14,18)*	15.4 (14,17)	17.4 (16,19)*
	REM	17.9 (17,19)	18.1 (17,19)	18.8 (18,20)	18.5 (17,20)
	Sleep latency, mean minutes (95% CI)	13.7 (12,15)	12.7 (10,15)	12.7 (11,15)	10.9 (9,13)*
	Sleep efficiency, % (95% CI)	84.0 (83,85)	85.1 (83,85)	6.0 (85,87)*	6.5 (85,88)*
	Total sleep time, minutes (95% CI)	374 (366,382)	380 (366,382)	392 (380,401)*	384 (373,394)
	Sleep fragmentation, minutes (95% CI)	13.7 (13,15)	14.4 (13,16)	13.9 (13,15)	15.3 (14,17)*
Freedman and Roehrs [31,32]		Pre-menopausal, N = 11	Menopausal no. hot flashes, N = 8	Menopausal, >6 hot flashes/24 hours, N = 12	
	Total sleep, ¯X hours (s.e.)	6.9 (0.7)	7.0 (0.4)	7.0 (0.4)	
	Sleep efficiency, % (s.e.)	87.2 (7.5)	88.5 (5.7)	87.6 (5.5)	
	Sleep latency ¯X minutes (s.e.)	18.3 (16.8)	17.2 (13.9)	20.2 (14.3)	
	Awakenings >1 minute, ¯X no. (s.e.)	4.8 (3.3)	6.9 (2.1)	6.7 (2.1)	
	Arousals ¯X no. (s.e.) sleep stages, % (s.e.): stage 1 stage 2, stage 3–4, REM	89.6 (30.1)	99.4 (45.8)	119.6 (45.8)	
	Sleep stages, % (s.e.):				
	Stage 1	9.3 (4.2)	10.5 (3.9)	10.4 (2.5)	
	Stage 2	54.0 (10.2)	55.9 (4.0)	56.3 (8.0)	
	Stage 3–4	14.4 (4–5)	14.4 (2–5)	16.5 (8.3)	
	REM	19.9 (4.4)	29.0 (3.0)	19.9 (5.4)	

*$p < 0.05$, compared to value for pre-menopause.

review of Krystal *et al*. It is noteworthy that both reviews, published 5 years apart, expressed concerns with the difficulty of interpreting small samples with different methods, use of one-dimensional questions to capture sleep disturbance and disorders, and had reservations about concluding that sleep problems are more common in menopause.

Several other insightful reviews were published between 2000 and 2006, providing a comprehensive description of individual studies conducted from 1976 to 2004. In general, the reviews continue to suggest that evidence for a role of menopause in sleep disturbance is not strong, but that findings indicate a trend in support of an association. Shaver and Zenk [20]

echoed the need for better definitions of menopause and also introduced the idea that there are subsets of menopausal women who may be more vulnerable to sleep problems, including those with vasomotor symptoms and high life stress. Landis and Moe [21], in their review in 2004, point out the widely observed decrease in sleep duration in recent years, and suggest that menopausal women may be among the groups that suffer the most sleep deprivation. It is possible that lack of adequate sleep due to balancing work and family responsibilities, emotional stress underlying grief of losing reproductive status, and effort needed to care for older relatives may be greatest at the age of the menopausal transition. The authors also point out the lack of information in past studies on specific sleep symptoms of insomnia, including problems initiating and maintaining sleep. Lack of specificity in the data on both menopause and sleep would, like random misclassification, tend to increase variance, making it difficult to detect true associations.

Woods and Mitchell [22] reviewed evidence from longitudinal studies of the menopausal transition begun in the 1990s, with "trouble sleeping" addressed in two of these studies. The authors stress the importance of understanding the trajectories of symptoms across the menopausal stages in assessing causal hypotheses and point to ongoing cohort studies that should eventually be able to address sleep across the menopausal transition. These include the Melbourne Women's Midlife Health Project, the Sleep in Women Across the Nation (SWAN) Study, the Penn Ovarian Aging Study, and the Seattle Midlife Women's Health Study. These cohort studies, plus the Sleep in Midlife Women Study of the Wisconsin Sleep Cohort, described in Appendix, deserve mention, as they all have a primary focus on sleep, proper sampling, and analytical methods. Of special importance, they do not have the limitations of poor specificity of previous studies in the measures of menopause and sleep, as detailed subjective and objective data are being collected longitudinally.

The most comprehensive review and synthesis of previous research and current thinking on menopause and sleep resulted from a recent NIH State of Science Conference on Management of Menopause-Related Symptoms [1, 2]. The conference panel addressed the question, "what is the evidence that symptoms reported by middle aged women are attributed to ovarian aging?" Approximately 30 possible symptoms and problems were considered, one of which was "trouble sleeping." The conference panel's statement was based on an evidence report (with structured literature review and conclusions) prepared for the Agency of Healthcare Research and Quality [2], research presentations during the conference, and panel deliberations. Interestingly, the conclusions of the evidence report [2] and conference panel statement [1] are somewhat inconsistent regarding associations of sleep and menopause.

The evidence report, based solely on published data [2], concluded vasomotor symptoms and vaginal dryness are symptoms most consistently associated with the menopausal transition, while sleep disturbance, somatic complaints, urinary complaints, sexual dysfunction, mood, and quality of life are inconsistently associated. The report noted that although results of studies are mixed, two good-quality cohort studies indicate that women have more difficulty sleeping as they transition through menopausal stages, and this may be due to vasomotor symptoms. The report summarized the prevalence of sleep problems by menopausal stages with ranges from 8 studies, published between 1969 and 2003. Prevalence ranges for sleep problems in pre- , peri-, and post-menopausal women were: 16–42%, 39–47%, and 35–60%, respectively; the report concluded there was a slight increase in the peri- and post-menopausal stages.

In contrast, the NIH conference panel statement, based on presentations and deliberations as well as the evidence report, concluded that there is "moderate evidence from longitudinal cohorts and cross-sectional observational studies that menopause is a cause of sleep disturbance in some women," stating "there is some positive evidence of a menopausal link for sleep disturbance." It was also noted that the role of vasomotor symptoms in sleep disturbance remains unclear, and that a conceptual framework is needed that includes social and cultural contexts. It is clear that the conference panel did not rely solely on interpretation of the evidence report, a carefully done structured review of past findings, but was influenced by positive findings from two prospective studies identified as "best evidence" (The Melbourne Women's Midlife Health Study [23] and the Australian Longitudinal Study of Women's Health [24]) and by oral presentations that introduced new perspectives. Although none of the presentations had sleep problems as the primary focus, abstracts available online indicate that sleep problems were discussed in the context of many symptoms [2]. (For program and abstracts,

see: http://consensus.nih.gov/2005/2005MenopausalSymptomsSOS025Program.pdf) Thus, from the earliest review to the most recent rigorous evidence report and scientific statement in 2005, the evidence for a role of the menopausal transition in diminished quality of sleep based on past research is still not adequate: findings from various studies lack agreement, in large part due to methodological limitations, time period differences, exclusion of women using HRT in many studies, and lack of attention to cultural differences. Most importantly, new questions directed at understanding and managing menopause relevant to women today and in the future have been raised.

Findings of recent population studies: does the menopausal transition contribute to sleep problems?

Studies with longitudinal analyses

The following two studies were identified by the evidence report for the NIH SOS conference to be good quality; the third study, based on the Seattle cohort, was judged fair. In the Melbourne Women's Midlife Health Project [24], a population-based sample of 438 women aged 45–55 years were followed annually for 7 years, beginning in 1991. Menopausal status was based on menstrual cycles. Six categories were used: pre-menopause, early and late peri-menopause, and 1, 2, and 3 years post-menopause. One hundred and seventy-two pre-menopausal women in the baseline sample became peri-or post-menopausal by the end of follow-up. Women were asked if they were bothered by trouble sleeping in the last 2 weeks, using a 4-point response scale. The severity of trouble sleeping showed a gradual increase across menopause categories (+6% between early and late peri-menopause).

The Australian Longitudinal Study on Women's Health [24] surveyed 8623 women aged 45–50 years in 1996 (baseline) and 1998. Menopausal status was based on menstrual cycle data and HRT use and six categories of baseline-follow-up status were used to capture change (pre-pre, pre-peri, peri-peri, pre-peri or post, etc.). A single question, "have you had difficulty sleeping in the past year?," with four frequency categories, was included as part of a multiple item check list. Multiple variable analysis was used to control for several potential confounding factors, and odds ratios were calculated for "sometimes or often frequency" of difficulty sleeping for women in the menopausal transition categories versus women who were pre-menopausal at both surveys. Odds ratios (OR) for difficulty sleeping with menopausal stage were statistically significant, but small in magnitude for women who became peri- (OR = 1.3), remained peri- (OR = 1.4), or became post-menopausal (OR = 1.5), or used HRT (OR = 1.5).

A subgroup of the Seattle Midlife Women's Health Study was begun in 1995 [25]. Three hundred and one women aged 35–55 years, considered pre- or peri-menopausal at the study onset, completed daily diaries for a 3-year period. Two sleep questions were used: trouble getting to sleep, and waking up in the night, with five frequency categories for response, as part of a 28-item symptom list. No association of sleep problems with menopausal stage was found.

Cross-sectional analyses

In a study published in 2003, Kravitz *et al.* [8] analyzed baseline data on menopausal status and sleep difficulty from a subset of the SWAN. The data were collected by in-person interviews of 2603 women, aged 40–55 years. On the basis of reported menstrual cycles, surgery, and HRT use, six categories of menopausal stage were created, and prevalence of sleep difficulty was based on the question, "Over the past two weeks, have you experienced difficulty sleeping? (Yes, no). Age-adjusted prevalence of difficulty sleeping was 31% in pre-menopause, 40% in early peri-menopause, 45% in late peri-menopause, 43% in natural menopause, 48% in surgical menopause, and 45% in post-menopause with HRT use. Of particular note, the prevalence of difficulty sleeping at each stage varied by ethnicity. In multivariable analyses, the odds ratios for difficulty sleeping and menopausal category, adjusted for sociodemographics, health status, and several other covariates, were small and statistically significant for only a few categories: late peri-menopause, natural post-menopause, and surgical post-menopause (all versus pre-menopause), with odds ratios ranging from 1.3 to 1.5. Results from this well-conducted, robust study showed a weak association of menopause and sleep problems, thus it appears that any bias from social or clinical influences regarding the expectation of poor sleep in menopause was low or nil. This is surprising, because the data were collected in 1995–97, a time of heightened attention to menopausal problems regarding sleep in the media.

Young *et al.* [26] reported on the only large study of menopause in which objective and subjective sleep

quality data were collected, the Wisconsin Sleep Cohort Study. A probability sample of 589 pre-, peri-, and post-menopausal women were studied with an overnight protocol that included polysomnography, and were queried on sleep satisfaction, usual experience with initiating and maintaining sleep, and excessive daytime sleepiness. Six semi-quantitative frequency categories, ranging from never to almost always, were offered for responses. Menopausal status was based on menstrual cycle history and changes, surgery, and use of HRT, with four categories resulting: pre-menopause, peri-menopause, post-menopause with HRT use, and post-menopause without HRT use. Mean values from polysomnographic data, adjusted for hot flash occurrence, sociodemographics, BMI, lifestyle, smoking, and other factors showed post-menopausal women not using HRT had significantly greater sleep efficiency (% of time in bed in documented sleep), more deep sleep, and had longer total sleep time compared with pre-menopausal women. Although differences were small, they were counter in direction to the hypothesis that sleep is worse in menopause. There was no measure of objective sleep quality, including distribution of sleep by stage, latency, and fragmentation, in which peri- or post-menopausal women without HRT use had worse sleep compared with pre-menopausal women (Table 3.3). In contrast, post-menopausal women who used HRT had slightly worse objectively measured sleep than did post-menopausal women who did not use HRT. The data were collected in the late 1990s to early 2000s, and it is likely that women who had the worst sleep choose to use HRT. This supports the theory of Shaver that there are subtypes of women who are more vulnerable to sleep problems.

Preliminary data and new perspectives

Preliminary data from longitudinal data collection on prevalence of sleep problems from the Wisconsin Sleep Cohort: Sleep in Midlife Women are included in Table 3.1. Findings are based on data from daily diaries completed by 262 women, over a 3–10-year period resulting in observation of 14939 woman-months. Diary data on menstrual cycle and other information was used to categorize each woman's menopausal stage and reported sleep problems (difficulty getting to sleep, waking up repeatedly, and restless sleep) for each month. For prevalence estimates, each sleep problem was defined as having the specific problem 2 or more nights/month. This definition was used to estimate prevalence most consistently with studies using the outcome measure of "any sleep problem in the past two weeks." Of note, although the prevalence of each sleep symptom does increase through the menopausal transition, the magnitudes differ by symptom. Among the problems, trouble with initiating sleep was the least prevalent, but was significantly higher in late peri- ($p = 0.02$) and post-menopause ($p = 0.001$) than in pre-menopause. The prevalence of difficulty maintaining sleep (waking up repeatedly) and restless sleep were higher across all menopausal status categories, and were comparable to the findings reported in Table 3.1 from studies using 1-item questions about trouble sleeping. Thus, it is likely that there are at least two important dimensions to subjectively perceived sleep problems in the menopausal transition: sleep onset and sleep maintenance.

Reports from cross-sectional data of the Wisconsin Sleep Cohort have shown increased odds of sleep apnea in post-menopausal compared to pre-menopausal women [27]. Preliminary analyses from the "Sleep in Midlife Woman" sub study, with biannual in-home polysomnography, continue to support the hypothesis that the risk of sleep apnea increases with advancement through the menopausal transition. In women with at least four in-home sleep studies, with woman-month as the unit of analysis, we estimated the effect of menopausal status on the apnea–hypopnea index (AHI, number of abnormal breathing events per hour of sleep), controlling for BMI, many other body habitus measures, education, exercise, sleeping position (i.e. % time on back), HRT use, initial age, and passage of time (i.e. aging). The severity of sleep apnea, indicated by AHI level, increased with passage through the menopausal transition. Compared to pre-menopause, women in early peri-menopause had 20% higher AHI ($p = 0.1$), 25% higher for late peri- ($p = 0.09$), and 43% higher for post-menopause ($p = 0.01$). These findings, although statistically significant for only post-menopause, indicate that underlying sleep apnea is more likely during and after menopause, and, as a distinct and treatable condition, must be considered apart from sleep problems in the constellation of "menopause symptoms."

Three of the ongoing cohort studies (SWAN, Seattle cohort and Penn Ovarian Aging Cohort) have examined the correlation of sleep problems, among other symptoms, with reproductive hormone levels

over time. Kravitz *et al.* [28] in the Daily Hormone Study, a subsample of SWAN participants, examined the relationship between sleep problems and hormones across the menstrual cycle in pre- and early peri-menopausal women (n = 630, ages 43–53 years). Diary data included nightly sleep problems, mood, vasomotor symptoms, and other items. The odds ratio, adjusted for age, ethnicity, and other factors, for trouble sleeping was 1.29 (95% CI = 1.00–1.65, p = 0.05) for peri- versus pre-menopausal women. Follicle stimulating hormone (FSH) was significantly related to trouble sleeping in the peri-menopausal group, while pregnanediol glucuronide was related to trouble sleeping in the pre-menopausal group. Thus, both stage and cycle phase were modifiers of a hormone link with trouble sleeping.

Woods *et al.* [29] reported data on a subset of women enrolled between 1990 and 1992 in the Seattle Midlife Women's Health Study. After initial interview, the sample of women has been followed over time, with data collected on menstrual cycle and symptoms by diaries and calendars, and in 1996 the women began providing first morning urine samples at various time intervals. Data from 41 women who had transitioned from early or middle stage of menopause to post-menopause (no menstrual cycle or spotting for 12 months) and provided data at 3 or more time points were selected for analysis (average follow-up = 6 years). Severity of early morning awakening and waking during the night was determined by average rating on a 5-point scale (none to extreme) over a 3-day period when urine was collected. The correlation of these sleep problems with levels of urinary estrone glucoronide, FSH, and testosterone were determined as well as correlations between all symptoms. Although hot flashes and a few other symptoms were related to one or more of the hormones, the sleep problems were not correlated with any of the hormones. However, both sleep problems were related to hot flashes and depressed mood. In line with an important new direction, the authors suggest that disturbed sleep due to factors other than menopausal hormone changes, including aging and underlying sleep disorders such as sleep apnea, may influence the occurrence of other menopausal symptoms, including hot flashes, mood, and cognitive symptoms. Others have described a "domino effect" with hot flashes leading to sleep disruption and, in turn, depressed mood [30]. However, Freedman and Roehrs [31, 32] studied a volunteer sample of women at various stages of menopause (based on STRAW) with EEG measures of sleep parameters including arousals, and hot flashes detected by sternal skin conductance. They found that women often had arousals prior to hot flashes, possibly due to underlying sleep disorders of restless legs and sleep apnea, and that hot flashes only during the first half of the night predicted subjective report of poor sleep. The best predictors of objectively measured poor sleep were, indeed, episodes of apnea, leg kicks, and brief arousals from sleep not due to hot flashes. Anxiety and hot flashes in the first half of the night predicted subjectively reported poor sleep.

Freeman *et al.* [33], in an analysis of the Penn Ovarian Aging cohort data, assessed the change in poor sleep and other symptoms over the menopausal transition with data from 10 assessment periods between 1997 and 2006, with a sample of 299 women followed for 9 years. Data were collected by interview on symptoms, menstrual cycle, and other factors, and blood samples were collected for hormone assays. Menopausal stage (using STRAW classification) was associated with hot flashes and body pain, but there was no association with poor sleep. Poor sleep was associated with decreased levels of inhibin b, a hormone that declines rapidly in the early menopausal transition. Consistent with the Woods *et al.* findings from the Seattle cohort, Freeman *et al.* noted that poor sleep was related to depressed mood, stress, and hot flashes. These authors noted that these findings are consistent with their in-depth study of sleep quality (submitted for publication), which did not worsen with menopausal stage alone, but was associated with reproductive hormones, hot flashes, depressed mood, and higher BMI. Furthermore, stress and depressed mood were strongly related to menopausal symptoms, including sleep problems. In a previous report, longitudinal findings from this study suggested that anxiety was a strong predictor of hot flashes. Taken together, new findings and some preliminary descriptions point to a perspective with sleep problems and mood influencing the occurrence and severity of other symptoms, including hot flashes. Investigators of these cohorts note that further longitudinal data will emerge on symptom interrelationships and hormonal changes, to uncover the sources of sleep complaints in those menopausal women that do experience them. This perspective varies from the notion that menopause *per se* affects sleep quality, in a general way. Rather, it supports a view of predisposing factors, including anxiety and underlying sleep disorders

that may influence the course of the menopausal transition.

In summary, over 30 years of research aimed at the hypothesis that reproductive hormone and other changes over the menopausal transition lead to diminished sleep quality have resulted in long tables of inconsistent findings and hesitancy in proclaiming that findings are conclusive. There are, however, many reasons why we cannot get answers from a grand meta-analysis of all the past studies. As underscored in the NIH SOS: Menopause panel report [1], the goal of current research is to develop clinical responses and self-care behaviors that will lead to women experiencing better-quality menopausal transition, both now and in the future. As discussed above, changes over time make past data less relevant in meeting this goal. And, in many past studies, women who used HRT were excluded from analyses, in order to look at natural menopausal states; at the peak of HRT use, almost half of some samples of midlife women were thus excluded from research studies. It is likely that these women differed in important ways from those not using HRT. For example, HRT users were likely to have more severe menopausal symptoms. Perhaps they had more sleep problems, coincident with menopause, that were exacerbated by, but not caused by, menopause. These women may have been more likely to have higher socioeconomic status and better access to health care. Thus, data on sleep during menopause in a large segment of midlife women is largely missing. Furthermore, much research was done on samples that comprised predominantly white women. In the sparse findings available, ethnic differences in the menopause–sleep relationship are seen. Thus, there are problems in generalizing past findings.

It is clear that we look to findings from the ongoing cohorts that include women with and without HRT use, surgical as well as natural menopause, samples with ethnic diversity, and which include definitions of both menopause and sleep problems with adequate specificity. There are important clinical implications from current thinking on sleep in the menopausal transition. Rather than focusing on menopause, particularly hormonal changes, as the hypothesized "cause" of sleep problems and thus the focus of treatment (i.e. HRT), researchers are stressing the need for a new conceptual framework to understand the role of sleep in the milieu of other symptoms over the menopausal transition. Wood and Mitchell (see pages 31 and 38 in: http://consensus.nih.gov/2005/2005MenopausalSymptomsSOS025Program.pdf) propose a conceptual model that includes information on symptom perception, sociocultural context, and personal characteristics to understand how sleep quality and other symptoms change over menopause, to understand symptom responses, and to devise management strategies. New findings that women with anxiety prior to menopause are at much higher risk of later experiencing hot flashes suggest that pre-menopausal characteristics may actually contribute to vasomotor symptoms, instead of the reverse pathway. Underlying undiagnosed sleep disorders, such as sleep apnea and restless legs syndrome, may further exacerbate hot flashes and other symptoms. Avis, in questioning a universal menopausal syndrome (see page 43 in: http://consensus.nih.gov/2005/2005MenopausalSymptomsSOS025Program.pdf), concludes that factor analyses argue against a single syndrome consisting of menopausal, psychological, and somatic symptoms, and that future research should focus on how symptoms are interrelated and whether there is a subgroup of women that can be identified who are more likely to have difficulties during menopause. At a time when HRT is not an immediate recourse to treating sleep problems in midlife women, it is critical that new paradigms be considered in developing new management strategies. New longitudinal studies that include psychological and sociodemographic data will allow the types of analyses mandated by new conceptual frameworks, and will hopefully result in new strategies to increase resilience to troublesome symptoms and increase quality of life during the menopausal transition. Most importantly, it is clear that underlying sleep disorders, including sleep apnea and restless legs syndrome, are prevalent in midlife women and should be identified and treated, rather than be dismissed as inevitable "menopausal symptoms" that will subside after the hormonal changes lessen in post-menopause.

Appendix

Ongoing cohort studies collecting detailed data on menopausal stage and sleep problems

1. The Melbourne Women's Midlife Health Project is based on a population sample of 438 women, aged 45–55 years, residing in Melbourne, recruited in 1991 by random digit telephone contact. Women who were

pre-menopausal and not using HRT or oral contraceptives were interviewed and followed annually. Menopausal status was based on menstrual cycles. Six categories were used: pre-menopause, early and late peri-menopause, and 1, 2, and 3 years post-menopause. Thus far, sleep measurement includes "trouble sleeping" in previous 2 weeks.

2. The Study of Women's Health Across the Nation (SWAN) is a large multicenter longitudinal study (cross-sectional component, >12 000, longitudinal sample n = 3300) developed in 1995 that specializes in ethnic diversity. The study will provide rich data on symptoms, life experiences, hormone levels, and other factors at yearly intervals for 10 years. Although the original sleep item included in the study was a dichotomous question on difficulty sleeping over the past few weeks, an ancillary study was added in 2003: SWAN Sleep, n=340 women, ages 48–59. Very detailed sleep data, added to the core SWAN data, were collected, including standard sleep disturbance scales and questions, actigraphy, and home polysomnography at baseline and at 3–4-year follow-up.

3. The Penn Ovarian Aging Study, begun in 1996, studied a cohort with initial sample size of 436 women aged 35–37 years. This study collects data on an impressive array of biological markers of menopausal changes. A highly sophisticated 5-year longitudinal protocol was added, as a separate NIH grant in 2005 based on the POAS sample and data, to include multiple nights of in-home polysomnography, upper airway MRI, and measures of upper airway dynamics including closing pressure

4. The Seattle Midlife Women's Health Study comprises a baseline sample of 508 pre-menopausal or early peri-menopausal women interviewed on menstrual status, menopausal symptoms, and other factors in 1990–1992. For the longitudinal cohort (n = 367), women were asked to complete an annual questionnaire, daily menstrual calendar, and health diary. The protocol was expanded to include collection of morning urine samples in 1996–2005. Three categories of menopausal status are used: early, middle (equivalent to STRAW early stage), and late. A 3-day diary was completed each month; sleep questions include early awakening and night-time awakening.

5. The Wisconsin Sleep Cohort: Sleep in Midlife Women Study was designed in 1996 with the primary aim of studying the development of sleep disturbance and sleep disorders, including sleep apnea over the menopausal transition. In the parent study (Wisconsin Sleep Cohort Study, begun in 1988), an in-laboratory protocol of polysomnography studies, serum samples, and many other tests and measures has been conducted at 4-year intervals. Of the 688 women in the cohort, a subgroup of 262 women at risk of menopause were studied with in-home polysomnography at 6-month intervals, to capture the menopausal transition and 2 years past the final menstrual period. The women also completed daily diaries, marking days of any menstrual bleeding and characteristics, difficulty with sleep onset, waking up repeatedly, or restless sleep, hot flashes, and reported monthly frequency of other symptoms including anxiety and depression, HRT, and other medication use. Menopausal status is categorized in a similar way to STRAW criteria, with pre-, early peri-, late peri-, post-, and duration (years) of post-menopause.

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Neuropsychology and neuroimaging of sleep-dependent memory processing: implications for aging

Matthew P. Walker

Introduction

An exciting renaissance is currently under way within the biological sciences, centered on the question of why we sleep, and focusing specifically on the role of sleep in learning, memory, and brain plasticity. Although this resurgence is relatively recent, the topic itself has a surprisingly long history. While several experimental attempts were made in the early nineteenth and twentieth centuries, it is only in the last 50 years, following the discovery of rapid eye movement (REM) and non-REM (NREM) sleep, that researchers began testing the hypothesis that sleep actively participates in processes of learning and memory [1, 2, 3]. With the establishment of sleep-dependent memory processing, an important and necessary next step is to begin understanding how sleep loss in later life may contribute to the known deterioration of memory function, and how these factors may interact – the topic of this chapter.

Memory categories, memory stages, and sleep stages

Before considering the relationship between aging, sleep, and memory, it is necessary first to outline the key components inherent to this question: memory systems, memory stages, and sleep stages.

While often used as a unitary term, "memory" does not represent a single entity. For example, human memory has been subject to several different classification schemes, the most popular being the distinction between declarative and non-declarative memory [4]. Declarative memory includes consciously accessible memories of fact-based information, and contains several subcategories, including episodic memory (memory for events in one's past) and semantic memory (memory for general knowledge) [4]. In contrast, non-declarative memory encompasses non-conscious memories, and includes subcategories such as conditioning, implicit memory, and procedural memory.

Just as memory is not monolithic, neither are the processes that create, sustain, and modify it. Instead, memories appear to evolve in several distinct stages over time. Memories are initially formed, or "encoded", by engaging with an object or performing an action, which in turn leads to the rapid (milliseconds to seconds) development of a memory representation. Yet following encoding, the memory representation remains susceptible to change or loss. To be maintained over longer intervals, a second stage termed memory "consolidation" is required [5], and appears to involve both local (cellular) and global (systems-level) mechanisms of plasticity. Following consolidation, a memory can be retained for days or years, during which time it can be recalled. But the act of memory recall itself is now believed to destabilize the memory representation, making it again labile and subject to potential degradation. Reconsolidation has therefore been proposed to transform the now destabilized memory back into a restabilized form. Thus, a vast array of intricate steps appears to be involved in the development, maintenance, modification, and recall of learned information.

Finally, it is important to keep in mind that sleep itself cannot be treated homogeneously, being divided into REM and NREM sleep. In primates and felines, NREM sleep has been further divided into substages 1 through 4, with stages 3 and 4 collectively referred to as "slow wave sleep" (SWS), based on a prevalence of low-frequency cortical oscillations. Dramatic changes in brain electrophysiology, neuromodulation, and functional anatomy accompany these alternating stages, demonstrating that sleep is equipped with a range of physiological and neurochemical states that can contribute differentially to learning and plasticity.

Memory encoding

Declarative memory encoding refers to the initial acquisition of information, whereby a memory trace of a specific event is created (milliseconds to seconds),

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which can support subsequent conscious recollection of that experience over time [3]. While somewhat simplistic, the processing steps of human memory encoding are believed to involve: (1) the transformation of sensory inputs into internal representations that are interpreted or comprehended; and (2) a subsequent process of binding these internal fragments into an enduring "memory trace". Over the past decade, significant advances in understanding the systems-level functional anatomy of memory encoding have occurred with the advent of functional neuroimaging technology. These studies have converged on structures within the temporal and prefrontal lobes [6], and more recently, the parietal lobe [7].

While early studies investigating the relationship between sleep and memory focused primarily on sleep after learning for consolidation [2, 8] (for relevance to aging and consolidation, see Chapter 5), more recent data have described the critical requirement of adequate sleep before learning for the initial formation or "encoding" of memory; the focus of this chapter. Before we discuss the potential interaction between aging, sleep loss, and memory impairments, it is first pertinent to summarize our current knowledge of human memory encoding.

Memory encoding in the healthy young brain

In standard imaging studies of human memory encoding, scanning is performed at the time of learning, with the efficiency of encoding measured by a later behavioral recall/recognition test. With the development of event-related functional magnetic resonance imaging (fMRI) (affording the ability to image discrete cognitive events), these investigations have become increasingly more refined, allowing the post hoc separation of individual encoding trials based on whether they are subsequently remembered or forgotten (reflecting successful or unsuccessful encoding attempts, respectively). Using this technique, a comparison of brain activity patterns between successful and unsuccessful encoding trials can be produced. This has become an established model of memory encoding known as the "difference due to memory" or "Dm effect" [6]; the neural signature of successful memory formation.

Using this technique, a considerable number of reports have shown that encoding of various material (e.g. visual, verbal, aural) is associated with robust and significant activation in both the prefrontal cortex (PFC) and medial temporal lobe (MTL), including the hippocampal complex (for reviews, see [6]). For example, in one of the earliest studies, Wagner and colleagues [9] reported greater verbal encoding activity in the parahippocampus and hippocampus, together with increased activation in left inferior PFC and fusiform cortex. Similarly, Brewer and colleagues [10] observed increased bilateral activity throughout the MTL during the encoding of complex visual scenes, together with increased right inferior PFC activity.

A multitude of studies have now replicated these encoding-related MTL activations, resulting in an emerging consensus that hippocampal activity at the time of learning reflects relational processing, binding disparate perceptual elements into a coherent memory representation. Therefore, high-level outputs from perceptual cortical regions during learning are directed to the MTL, which integrates these elements in the service of producing a bound episodic memory representation. Different combinations of neocortical circuits can thus potentially interact with the MTL, and which specific perceptual regions appears to be a function of the nature of the event being encoded. Furthermore, the PFC, including dorsal lateral and inferior regions, is believed to influence encoding by modulating perceptual cortical processing, by way of information selection and, in doing so, regulates specific input to the MTL for representational binding.

Memory encoding in aging

While age-related brain atrophy, including decreases in brain volume and white matter density, undoubtedly plays a role in the progressive decline of memory with age [11], correlations between cognitive performance and structural change have been inconsistent. This would indicate a difficulty in accurate memory prediction using such measures [12], leading to the concept that functional differences, in addition to structural changes, play a role in cognitive aging. A leading hypothesis to explain age-related deterioration of memory has focused on processes of MTL binding, and their progressive failure in the elderly. A number of neuroimaging studies have shown decreased MTL involvement during memory formation in older adults, compared to young adults. Interestingly, associated with these MTL deficits are corresponding increases in PFC regions in older adults, beyond those observed in young populations. Furthermore, these increases are often observed bilaterally,

commonly in the left and right inferior frontal regions [13, 14, 15], whereas encoding in young subjects often results in more lateralized activity. The extent to which these frontal changes represent functional or dysfunctional aging remains debated. For example, using verbal memory tasks, Cabeza *et al.* [16] and Rosen *et al.* [17] both found that older adults expressing superior encoding performance elicited bilateral PFC activity, whereas low-performing elderly participants (and young subjects) exhibited only unilateral activations. Reuter-Lorenz *et al.* [18] also found that higher functioning elderly subjects exhibited more PFC bilaterality during a verbal learning task than lower functioning elderly participants. Other cases, however, have suggested that these additional PFC activations may be non-functional, with bilaterality more characteristic of the participant's age and not necessarily superior performance [19, 20].

Utilizing the "difference due to memory" paradigm, Gutchess and colleagues [21] have recently tested this hypothesis, examining whether the extent of MTL impairment during encoding in older adults is associated with a proportional increase in compensatory prefrontal activity, and superior performance. Focusing on the Dm effect (by subtracting forgotten items from remembered items), younger and older adults both demonstrated activation of inferior frontal and lateral occipital regions. However, older adults showed significantly less activation than young adults in the left and right posterior hippocampus (Figure 4.1a). In contrast, older adults expressed significantly more activation than young adults in the bilateral PFC (Figure 4.1b). Moreover, correlations between inferior PFC activity and hippocampal activity were significantly negative for old but not young participants, suggesting that older adults expressing the least hippocampal activity during encoding correspondingly displayed the strongest inferior PFC activation. This has led to the assertion that additional PFC recruitment represents a functional compensatory response to reduced hippocampal encoding activity in older adults. Most interestingly, as outlined below, we have reported remarkably similar posterior hippocampal impairments and associated PFC changes during memory encoding, but in young sleep-deprived subjects (see [22], and Figure 4.3 and Figure 4.4 for comparisons). These concordant findings suggest that age-related changes in encoding may not be entirely due to age, but, instead, the inadequate sleep that accompanies it – a potentially treatable circumstance.

In summary, the initial act of learning requires a process of information perception and subsequent amalgamation of this experience into a coherent memory representation. A volume of work has demonstrated that, for human declarative memories, this process is achieved by co-ordinated hippocampal binding of information across disparate cortical regions at the time of learning, the contents of which are guided by the prefrontal cortex. With age, this process appears to deteriorate, resulting in significantly less encoding-related activity in hippocampal regions, and corresponding compensatory efforts in bilateral prefrontal activation.

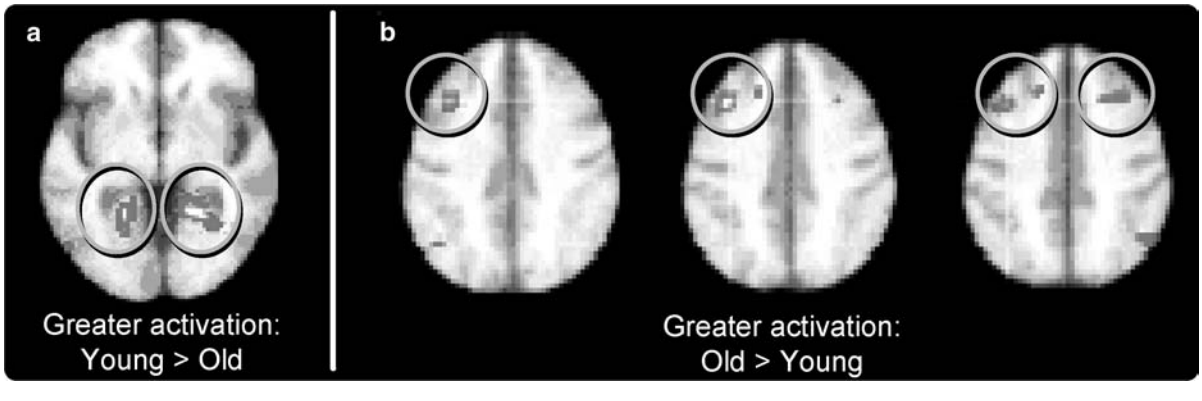

Figure 4.1. Encoding-related activation differences between young and elderly participants: (a) Young subjects exhibited significantly greater activation in posterior hippocampal regions, while (b) older adults demonstrated significantly greater bilateral prefrontal activation. See plate section for color version. (Adapted from Gutchess AH, Welsh RC, Hedden T, *et al.* Aging and the neural correlates of successful picture encoding: frontal activations compensate for decreased medial-temporal activity. *J Cogn Neurosci* 2005;**17**(1):84–96.)

Sleep and memory processing

Sleep and memory encoding

One of the earliest studies to report the effects of sleep deprivation on declarative memory encoding in humans was by Morris *et al.* [23], indicating that "temporal memory" (memory for when events occur) was significantly disrupted by a night of pre-training sleep loss. These findings have been revisited in a more rigorous study by Harrison *et al.* [24], again using the temporal memory paradigm. Significant impairments in retention were evident in a group of subjects deprived of sleep for 36 hours, who scored significantly lower than controls, even in a subgroup that received caffeine to overcome non-specific effects of lower arousal. Furthermore, the sleep-deprived subjects displayed significantly worse insight into their memory encoding performance, resulting in lower predictive ability of performance.

Pioneering work by Drummond *et al.* [25] has directly examined the neural basis of similar behavioral impairments using fMRI, investigating the effects of 35 hours of total sleep deprivation on verbal learning. In the sleep-deprived group, regions of the MTL were significantly less active during learning, relative to the control group, while the prefrontal cortex actually expressed greater activation – findings that parallel those seen in aging. Most interestingly, the parietal lobes, which were not activated in the control group during learning, were significantly active in the deprivation group. These findings confirm that sleep deprivation in young adults induces a robust behavioral impairment in verbal memory formation, the neural mechanisms of which may be mediated by a dynamic set of bi-directional changes – an inability of the medial temporal lobe to engage normally due to sleep loss, combined with compensation attempts by prefrontal regions, which in turn may facilitate recruitment of parietal lobe function [26].

Most recently, we have investigated the impact of sleep deprivation on the neural and behavioral ability to form new human episodic memories [22]. A group of young healthy subjects were either deprived of sleep for 36 hours prior to an encoding session (Sleep Deprivation group), or slept normally (Sleep Control group). At the encoding session, performed during fMRI scanning, subjects were presented with 150 picture stimulus trials and asked to provide an indoor/outdoor behavioral response to each. Two days later, following two nights of recovery sleep, subjects returned for a surprise memory recognition task (performed without MRI scanning) to evaluate the effectiveness of initial memory encoding. During this recognition test, the original 150 stimuli were shown, together with 75 new pictures, and subjects made a forced choice old/new memory decision for each.

Memory performance in the Sleep Deprivation group was significantly worse than the Sleep Control group at later testing, with mean recognition levels demonstrating a significant 20% deficit under conditions of sleep deprivation, relative to a normal night of sleep. Therefore, at a performance level, there was behavioral confirmation of impaired declarative encoding following a night of sleep deprivation, resulting in less enduring memory representations. Turning to the neuroimaging data, encoding-related activation patterns were first contrasted between the two groups, thereby identifying the consequential differences resulting from a night of sleep deprivation, relative to having slept normally. No significant differences were identified in prefrontal, parietal or occipital regions. However, a significant decreased level of activation was evident in bilateral posterior hippocampal regions in the Sleep Deprivation condition, compared to the Sleep Control condition (Figure 4.2). These findings demonstrate that, in the state of sleep loss, there is a selective and significant impairment within the MTL and hippocampus in particular – deficits that are associated with a reduced capacity for memory formation.

Regarding these group differences in brain activity, it is of note that memory performance was different between the two groups. To further explore these performance effects, memory recognition score was regressed with corresponding brain activation in each group separately. Rather than both groups demonstrating a similar correlative network of activity with memory performance along one continuum, different frontal lobe regions emerged. In the Sleep Control group, increasing memory performance across subjects showed a strong positive relationship with the extent of activation in the right dorsal/middle lateral prefrontal cortex (Figure 4.3a). In contrast, a region in the right inferior frontal gyrus (IFG) displayed a significant positive, potentially compensatory, relationship with memory performance in the Sleep Deprivation group (Figure 4.3b). Therefore, in addition to the main group-level differences in hippocampal activity, there was also evidence for unique performance-related networks in each condition, with

the extent of memory encoding being associated with activation in specific prefrontal cortex (PFC) regions.

Together, these results describe a marked deficit in the neural ability to encode new human memories without adequate prior sleep. Common across the group comparisons were impairments within the hippocampal complex – a region known to be critical for learning new episodic information. It would therefore appear that sleep is not only important after learning for the subsequent consolidation of memory [2], but that sleep before learning is equally critical in preparing the brain for next-day memory formation. Also of note, a considerable number of neuroimaging studies to date have demonstrated that, in well-rested subjects, the magnitude of activity in the PFC during learning, including medial and lateral regions, can predict the degree of encoding success. We found similar relationships in subjects that had slept normally the night before learning, with the extent of encoding efficiency across subjects being proportional to activation in the right middle/dorsal PFC. In contrast, only activity within the right IFG, and not dorsal and middle lateral prefrontal regions, demonstrated a correlation with encoding success in subjects who had been deprived of sleep. This significantly altered pattern of activity may represent a compensatory attempt when hippocampal – and consequently lateral prefrontal – regions fail to activate normally in the state of sleep deprivation. Most pertinent to this chapter, these impairments in hippocampal encoding activity, and alterations in prefrontal response, show a remarkable degree of correspondence with changes in encoding activation reported in elderly cohorts (see Figure 4.1 for comparison). These parallels suggest that the signature neural and behavioral memory impairments observed in later life may reflect a potential association with impaired sleep, rather than simple age itself, and, if validated, represents a treatable situation once the mechanisms of sleep-dependent memory processing have been resolved.

Mechanisms of sleep-dependent memory processing

Several electrophysiological signatures of sleep, reflecting synchronized oscillatory patterns of neuronal activity, can actively promote memory processing, and may represent future targets in aging-intervention strategies.

Perhaps the most abundant evidence has focused on the role of NREM slow oscillations and sleep spindles. Sleep spindles are bursts of coherent brain activity, visible in the EEG, and are most evident during stage 2 NREM sleep. They consist of brief 11–16 Hz waves lasting 0.5–1.5 seconds. In animals, these thalamo-cortical events tend to co-occur with significant excitatory activity initiated in the hippocampus, termed the "hippocampal sharp wave-ripples." This co-occurrence of hippocampal sharp waves and cortical spindles has been proposed to underlie the integration of information between the hippocampus and neocortex as memories are processed during sleep [27]. In support of this hypothesis, several human studies have shown a correlation between hippocampus-dependent

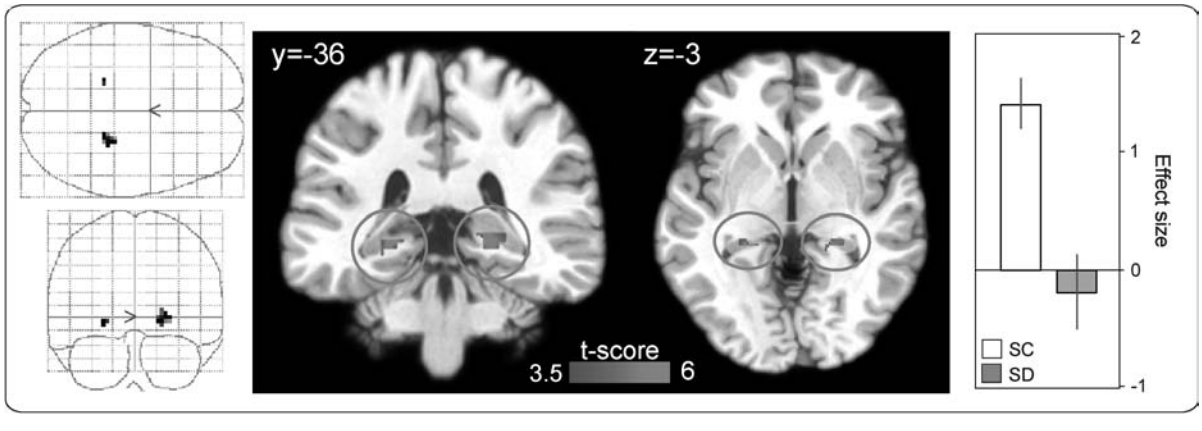

Figure 4.2. fMRI encoding deficits – all trials. Regions of decreased activation in the Sleep Deprivation (SD) group relative to the Sleep Control (SC) group in bilateral posterior hippocampus. From left to right are color displays of significant difference (circled; coronal and axial slices, respectively), together with a histogram of parameter estimates (effect size) of averaged hippocampal activity. Effects are significant at $p<0.001$; >5 contiguous voxels. See plate section for color version.

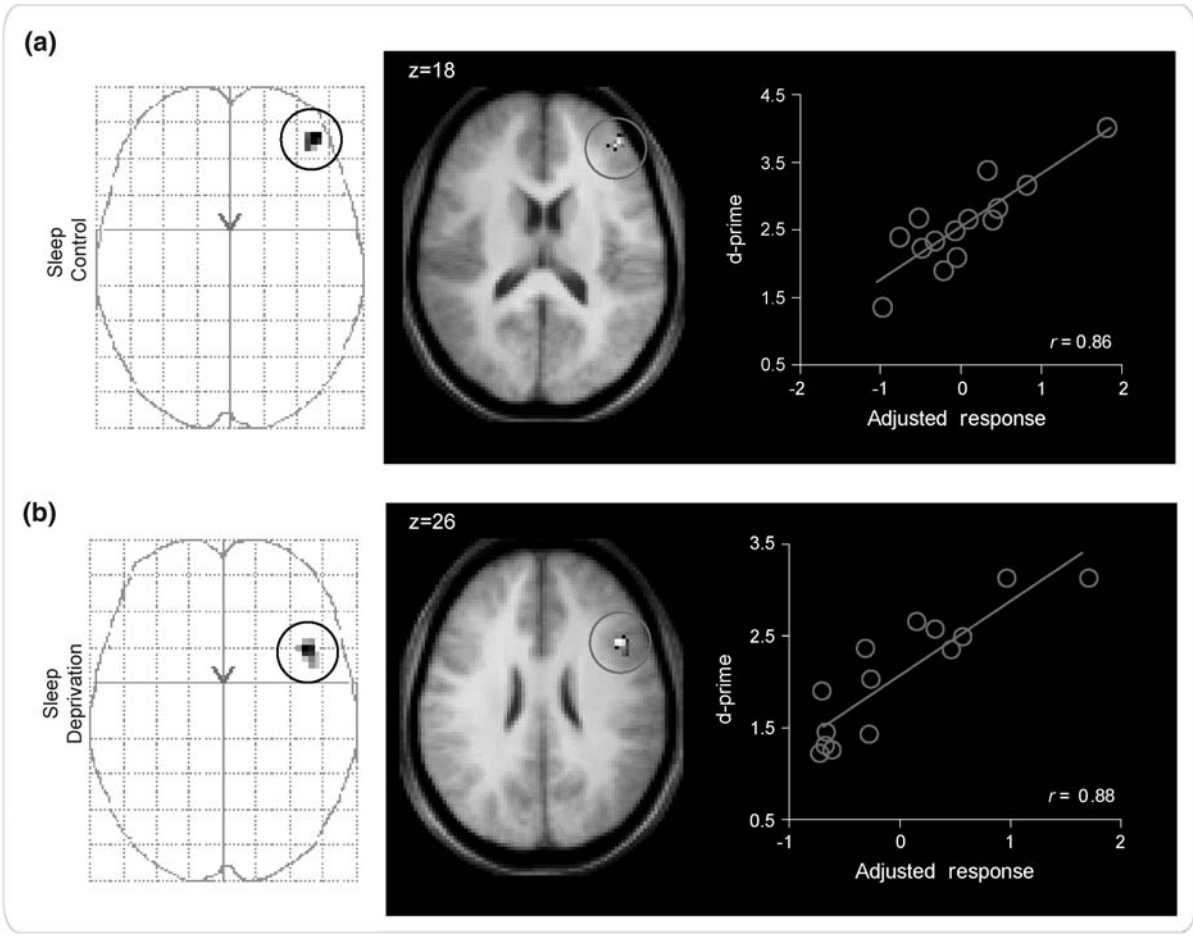

Figure 4.3. fMRI correlation analysis with memory performance. Regions of significant correlation between encoding-related activation and memory performance (d') across subjects in: (a) The Sleep Control group (peak – right middle/dorso-lateral prefrontal cortex); and (b) The Sleep Deprivation group (peak – right inferior frontal gyrus). Left of each panel are glass brain MIP plots. Middle of each panel are corresponding color displays of significant correlation (circled) on axial slices. Right of each panel are plots of individual subjects' memory performance with adjusted response from the peak voxel. Effects are significant at p<0.001. See plate section for color version.

episodic learning and sleep spindle characteristics. In one such study [28], subjects encoded a list of word-pairs 1 hour prior to sleep, which resulted in a 34% increase in spindle density in the first 90 minutes of sleep, relative to a control condition (letter counting of word-pairs, without substantial learning). Moreover, the magnitude of spindle density increase was positively correlated with a recall tested immediately after learning just before bed, and with a delayed recall test the next morning. These findings mirror previous observations by Meier-Koll *et al.* [29], who reported a similar increase in spindles following learning of a hippocampus-dependent maze task, and by Clemens *et al.* [30] who found a correlation between spindle density and overnight declarative verbal memory retention.

In addition to sleep spindles, slow wave oscillations, including both classical delta activity (1–4 Hz) and the more recently characterized "cortical slow oscillation" (<1 Hz), have been implicated in memory consolidation. This slow oscillatory activity in neuronal networks may allow distant ensembles to become co-operatively synchronized, thereby binding and consolidating memories dispersed across distant brain regions. Cortical slow oscillations have been observed in humans and in conjunction with increased EEG coherence. For example, Molle *et al.* [31] recently demonstrated that increased EEG coherence, which was strong during the initial encoding of declarative memory (learning of word-pairs), reappeared with cortical slow oscillations during subsequent NREM

SWS. Interestingly, while there were only marginal increases in coherence when measured over all NREM sleep, this coherence was dramatically increased when the analysis was time-locked to the occurrence of the cortical slow oscillation itself [31]. Such findings suggest that slow oscillations are important to the reprocessing of memories during sleep for two potentially significant reasons. First, it suggests that high coherence between EEG signals from different sites on the scalp reflect an increased interplay between the underlying neuronal networks that may represent different components of the memory trace (e.g. perceptual, temporal, spatial, and relational components), and second, it indicates that efficient declarative encoding of episodic associations is facilitated by the large-scale synchrony of cortical neuronal activity measured by EEG coherence.

Interestingly, slow oscillations also appear to exert a grouping influence over spindle activity. For example, it has been demonstrated that during human SWS, rhythmic activity in the spindle frequency range appears to positively correlate with periods of slow oscillations [32]. Moreover, discrete spindles identified during NREM strongly coincide with the depolarizing portion of the cortical slow oscillations, and are themselves preceded by pronounced hyperpolarizing waves [32]. These results suggest that slow rhythmic depolarizations and hyperpolarizations (the so-called "up" and "down" states of the cortex) might respectively drive and inhibit thalamically generated spindle activity, and in doing so, act as the master orchestrator not only of coherent cortical oscillations, but in addition, the regulation and control of subcortical thalamic spindle activity.

How could this co-operative mechanism promote the plastic neuronal changes that underlie memory processing? One plausible mechanism might involve calcium transients mediated by spindle activity. Not only is spindle activity hypothesized to trigger massive Ca^{2+} influx into neocortical pyramidal cells, but there is also evidence that repeated spindle-associated spike discharges can trigger long-term potentiation in neocortical synapses [33]. As synchronous spindle activity occurs preferentially at synapses previously potentiated by tetanizing afferent stimulation, slow oscillation-driven spindle activity might contribute to the strengthening of synaptic connections in neocortical circuitry, and by doing so, restore next-day hippocampal encoding ability for new learning.

Perhaps the most compelling evidence for this model to date was a recent report that experimentally enhanced human prefrontal slow oscillations, and, as a consequence, improved memory function [34]. Using a technique called direct current stimulation (DCS), Marshall and colleagues induced slow (0.75 Hz) oscillation-like field potentials in healthy young subjects during early NREM sleep, following learning of an episodic memory task (word-pairs). Relative to the sham condition (or theta stimulation), the DCS not only increased the amount of emerging slow wave sleep during the simulation period (and for some time after), but significantly enhanced the retention of the hippocampus-dependent declarative memories. Interestingly, in addition to the facilitation of endogenous cortical slow oscillations, the stimulation also increased the amount of spindle activity in the frontal cortex. Such findings indicate that endogenous slow oscillations, in combination with co-ordinated spindle activity, may play a causal role in sleep-associated memory processing.

Thus, when viewed as a set of functional oscillatory patterns, rather than separate, co-ordinated slow oscillations and sleep spindles, this offers a mechanistically plausible model allowing the hippocampus and neocortex to integrate new information into long-term memory during sleep [35]. This co-operative model has two critically important functional consequences: (1) assisting the co-ordinated transfer of newly encoded episodic hippocampal memory traces into distributed neocortical regions; and, as a consequence, (2) "refreshing" or restoring hippocampal encoding capacity, affording improving learning ability the next day.

In recent years, an orthogonal plasticity model of slow wave sleep has emerged, termed the "synaptic homeostasis model" [36]. The orthogonality of the model to that described above lies in the mechanistic consequence of slow wave activity – proposed not as an oscillation co-ordinating the transfer of memory, but instead, as a neurophysiological state that actively promotes synaptic downscaling by way of the long-term depression (LTD) of neural connections. According to the hypothesis, plastic processes, such as learning occurring during wakefulness, result in a net increase in synaptic strength in numerous brain circuits. The role of sleep, and the slow oscillation in particular, is proposed to selectively downscale synaptic strength back to a baseline level, and in doing so, sculpt more efficient memory representation. Most pertinent, this model not only predicts a more refined and strengthened memory trace (the basis of memory

consolidation), but equally critical, also prevents a situation of synaptic over-potentiation, resulting in saturated plasticity that would effectively negate new learning the next day.

To date, a number of human studies have provided evidence supporting this model, demonstrating that, following new learning, there are topographically and locally specific increases in cortical slow wave activity (SWA), the extent of which is proportional to the amount of prior learning [37]. Furthermore, experimentally impairing the amount of experience-dependent learning during the day triggers the opposite effect – topographically reducing the amount of SWA in associated cortical regions [38]. These findings offer support for the concept of sleep-dependent neural pruning, the goal of which is to regulate neural circuitry involved in learning at an anatomically specific level, mapping to the corresponding memory representation.

In summary, much evidence to date implicates slow wave activity as well as spindle oscillations in learning and memory processing. Although there may not be a consensus on which of the above specific models is correct, or whether both function symbiotically, these models indicate a significant benefit of NREM oscillatory activity in supporting brain plasticity (either strengthening or weakening). Such theories make very clear and relevant predictions; impairments in SWS and/or spindle activity will compromise the regulation of overnight homeostatic memory processing, and in doing so, will significantly reduce the capacity for next-day encoding of new memories, the implications of which we now address in aging.

Sleep and aging

Although there has been a strong focus in recent years on the role of sleep in memory processing, the implications of age-associated sleep loss and memory deterioration across the lifespan have been largely neglected. This is perhaps surprising, considering that sleep difficulties are a prevalent and well-documented problem in later life, and at the same time, memory function, and declarative memory in particular, also declines with age [39]. But while sleep disruption in the elderly is not disputed, it is often mistakenly considered a normal part of aging (see associated chapters for more detailed reviews).

The inability to initiate sleep, nocturnal waking, difficulty maintaining sleep, rising too early, and increased propensity for daytime napping ranked among the chief sleep complaints of older adults, reported in over 55% of the elderly [40]. Compositionally, stage-2 NREM remains somewhat unchanged across the adult lifespan, and REM sleep exhibits a gradual decline. The pre-eminent change with aging appears to be a significant decrease in NREM SWS. This decline actually begins in the late 20s to early 30s, but by age 60, SWS amounts have dropped to approximately 5% of total sleep time. Parallel to this SWS decrease is a rise in wake-time throughout the night, increasing from 4% to 5% in middle-age to approximately 15% in the elderly.

One alternative explanation for this dramatic SWS decrease in later life may be the rigid scoring criterion used in sleep staging, requiring a specific EEG slow wave. Consequently, slow wave activity (SWA; power density in the 0.5–3.0 Hz range) may not be dissimilar in quantity to younger populations. However, this does not appear to be the case; several studies have now demonstrated that the intensity of NREM EEG delta power, in addition to classically scored NREM SWS, likewise declines systematically over the lifespan [41]. As a result, delta EEG power at age 70 is approximately 50% of that observed at age 20. Therefore, a neurophysiological signature of human aging may be the decreased ability to obtain and potentially generate NREM SWS, either measured by visual sleep-stage scoring, or using quantitative EEG analyses, such as SWA.

The relevance of spindles and their role in memory processing becomes particularly germane in the context of aging based on accumulating evidence of decreased spindle activity in the elderly. Comparisons among young and middle-aged adults and the elderly have generally indicated a decrease in spindle measures with age, including both visually scored spindles and their automatic detection. The dynamics of spectral power in the sigma frequency range have also shown similar age-related decreasing trends, and may be particularly prominent in the frontal lobe (especially left PFC regions [42], which, parenthetically, are the same regions most commonly implicated in human memory formation, and undergo age-related changes in encoding-related patterns of brain activation). Moreover, the well-characterized increase in spindle density across NREM sleep episodes in younger age-range populations has been shown to be compromised in older cohorts above the age of ~65 years [42]; a finding that may be due to aging brain pathology, rather than simply a consequence of reduced

sleep efficiency. Thus, in addition to the hallmark changes in SWS with age, marked and perhaps consequential changes in sleep spindles also appear to take place. The topographical age-related sleep difference is likewise significant in the current context of memory, since it is the co-ordinated interaction between hippocampal and prefrontal regions through SWA and spindle mechanisms that is believed to underlie episodic sleep-dependent memory processing.

An obvious question is what, if any, consequence such altered sleep has on cognitive function in the elderly, and on memory encoding specifically. While a number of studies have investigated the cognitive consequence of poor sleep in later life, no studies to date have expressly tested the hypothesis that sleep decline in later life, particularly reductions of NREM SWS, are associated with an impaired neural and behavioral ability to form new memories. However, the confluence of the above fields does allow the development of a working model of age-related sleep loss and the reduced capacity for new learning. While admittedly simplistic, this model affords specific predictions about the regional changes, type of memory impairment, and potential recovery that may occur as a consequence of sleep alterations in aging.

The nexus: a functional hypothesis of sleep, memory, and aging

Based on a synthesis of these two research areas (sleep-dependent memory processing and age-related memory impairment), a testable, functional anatomical model of human memory formation and the impact that age-related sleep loss may impose is outlined below. It is important to point out, however, that the cause of mental decline in aging is a multivariate one, and it is not suggested here that aging is exclusively a sleep-related problem. Cognitive aging is known to be associated with a number of identified intrinsic features (e.g. neural atrophy, reduced blood flow), as well as extrinsic factors (e.g. social interaction, daily intellectual engagement). However, this model sets forth a previously unconsidered factor contributing to memory impairment in the elderly, and one that, from a clinical standpoint, is potentially treatable. The goal of this model is to contribute a new perspective in the understanding of human aging and the complications that impair memory function in later life, and, in doing so, offer new translational targets for treatment therapies.

Model conjectures

The hippocampus is widely acknowledged as a key fulcrum of declarative memory encoding, performing the service of binding disparate perceptual cortical information at the time of learning. As discussed above, we and others have provided evidence that this same structure, the hippocampus and surrounding parahippocampus, is selectively impaired by the state of sleep deprivation and, as a consequence, renders a significant deficit in memory encoding. Although the mechanistic cause of this hippocampal deficit remains unknown, we have entertained two possibilities [39]. The first is that the process of sleep loss results in the accumulation of biological factors that actively inhibit neural function, thereby compromising task-related hippocampal encoding ability. The second concerns the proposed hippocampal–neocortical model of memory transfer – the relocation of recently encoded information from the short-term storage capacity of the hippocampus to the larger storage reservoir of the neocortex [43], a process that appears to occur most preferentially during sleep, specifically NREM SWS in co-operation with sleep spindles. However, if the occurrence of these neurophysiological oscillations is subverted, transfer of prior daytime information from the hippocampus would be negated and, as a consequence, render a diminished capacity for additional hippocampal encoding the next day. Furthermore, this requisite for NREM SWS may also pertain to the PFC. These slow oscillations of frontal origin are suggested to play a fundamental role in synaptic homeostasis, "pruning" over-potentiated cortical networks resulting from the day's experience, and resetting optimal brain connectivity [36]. Without the opportunity to depotentiate saturated networks due to a reduction or loss of NREM SWS, a significant decrease in PFC functional efficiency would be predicted. These insights offer the first conjecture of the model (Figure 4.4a), describing the essential need for sleep before learning, specifically NREM SWS, thereby optimizing hippocampal encoding capacity, and may also pertain to associated PFC function, allowing efficient next-day memory formation.

The second model conjecture applies these insights to the known age-related impairments in memory, described in the section on "Memory encoding in aging". Deterioration of hippocampal function has long been considered a leading cause of memory

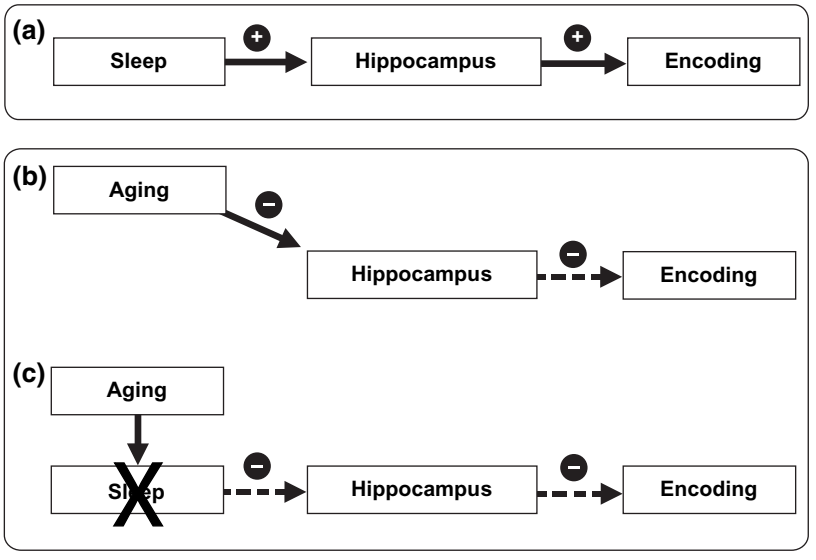

Figure 4.4. Model of sleep, memory encoding, and their failure with age. (a) Prior sleep, specifically NREM SWS in conjunction with spindles, "primes" the hippocampus for next-day memory encoding. (b) Deterioration of hippocampal function as a direct consequence of age is hypothesized as a principal candidate for the failure of memory encoding. (c) Contrary to this, this model suggests that NREM SWS and spindle dysregulation due to aging, and not aging itself, is responsible for reduced hippocampal function and impaired memory.

decline in later life, as well as certain degenerative dementias. Indeed, as illustrated in Figure 4.4b, it is the process of aging itself that is believed to impair functional integrity of the hippocampal complex. However, rather than being a direct consequence of aging, this model implies that such deficits are, at least in part, a consequence of dysregulated sleep. Specifically, the inability to initiate, maintain, and generate sleep in the elderly results in the curtailment of NREM SWS and the potential reduction in spindle generation, preventing the required overnight hippocampal and cortical dynamics (described above) necessary in preparing the brain for subsequent memory encoding. As a consequence, there exists a reduced capacity for learning new information (Figure 4.4c). However, unlike the classical model of age-related memory decline, this situation is potentially treatable, and by re-establishing sleep quality and quantity, a significant recovery of memory function would be predicted.

The final conjuncture is the targeted restoration of sleep, and hence the remediation of memory ability in the elderly. To achieve this goal, we will need to first characterize: (1) whether impaired memory encoding at a neural and behavioral level in later life is not simply associated with age-related sleep loss, but actually caused by this disruption; and (2) whether pharmacological treatments as well as ecologically valid, non-pharmacological interventions (e.g. daytime naps) are able to restore the functional ability for memory encoding.These are the challenges that now lie ahead.

Concluding summary

Sleep is widely recognized as an important factor governing processes of memory and brain plasticity. Most recently, adequate pre-training sleep has been implicated in preparing the brain for next-day memory encoding, priming key medial temporal lobe structures for efficient learning. Independent of these factors, both sleep and memory are known to deteriorate with age. However, these changes have been considered simply as co-occurring phenomena. Here we outline the reasoning for such a link, and suggest it is, in part, a causal (and treatable) association. Work across the neurosciences will be necessary to test this hypothesis at both a neural and behavioral level. By way of such a multidisciplinary approach, we can address perhaps the most important horizon quest: translating basic findings into clinical action, and understanding how disease and pathology stemming from aging can be understood on the basis of sleep-dependent memory failure.

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Sleep and memory in the elderly

Orla P. Hornung

Introduction

The significance of sleep for memory consolidation is presently a topic of great interest within the neurosciences and follows a long tradition in psychological research. More than 200 years ago, the English psychologist David Hartley proposed that dreaming might alter the strength of associative links within memory [1]. In 1914, Rosa Heine from the Psychological Institute of the University of Göttingen reported that nonsense syllables learned immediately before sleep were better recalled after a retention interval of 24 hours than those with a period of wakefulness intervening between learning and sleep [2]. Ten years later, John Jenkins and Karl Dallenbach from the Psychological Laboratory of Cornell University compared the effect of sleep on memory retention for nonsense syllables to that of wakefulness and found that it was more favorable to sleep after learning than to stay awake for an equally long period of time [3]. A large body of research has evolved in the meantime and the relationship between sleep and memory has remained an active topic of research within the field of psychology and the neurosciences until today [4]. It is of interest to note that the current state of knowledge in this field of research would not have been reached if it had not been for two important milestones in the study of sleep and memory. First of all, the discovery of rapid eye movement (REM) sleep by Eugene Aserinsky and Nathaniel Kleitman in 1953 contributed to a fundamental reconceptualization of sleep as an active and heterogeneous process [5]. In addition, the classification of different memory systems and findings, with regard to their neural substrates, have led to significant new developments in the experimental design of sleep and memory studies (see, for example, [6, 7]).

As an unprecedented number of people reach late adulthood today, public concern about the consequences of this demographic development grows. In Germany, for example, dementia affects less than 2% of older adults between the ages of 65 and 69 years, while more than 30% of people over the age of 90 years are afflicted by the disorder [8]. Moderate or severe insomnia is reported by 27% of women and 14% of men between the ages of 18 and 79 years in Germany, with the prevalence of severe insomnia strongly increasing from young to late adulthood [8]. Severe insomnia is reported by only 2.5% of women and 0.7% of men between the ages of 20 and 29 years, which corresponds to 13.2% of women and 5.2% of men aged 70 to 79 years. In light of these findings, research with regard to sleep and memory processes in old age serves current endeavors in society and science to find ways of preserving and promoting cognitive functioning across the lifespan.

Basic background

The central research topic of this chapter is embedded within three major fields of research, i.e. sleep, memory, and cognitive aging research. In order to fully appreciate the scope of the central research topic, it is useful to have a basic understanding of sleep stages and sleep architecture as well as concomitant changes in neurochemistry and brain activity. In addition, it is of advantage to have some prior knowledge about the classification of memory systems and stages of memory consolidation. Finally, information with regard to different trajectories of neurocognitive aging is of great interest when studying memory processes in old age.

Sleep stages and sleep architecture

According to the standard scoring system for stages of sleep published by Rechtschaffen and Kales in 1968 [9], human sleep is characterized by three basic polysomnographic measures, i.e. electroencephalography (EEG), electro-oculography (EOG), and electromyography (EMG). Based on these three measures, sleep has been broadly classified into REM sleep and non-REM (NREM) sleep, with NREM sleep being further

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divided into stages 1 to 4 NREM sleep, corresponding to increasing depth of sleep. Stages 3 and 4 NREM sleep, reflecting the deepest stages of NREM sleep, are often subsumed under the term slow wave sleep (SWS).

During the course of night-time sleep, NREM sleep and REM sleep alternate within an ultradian cycle of approximately 90 minutes' duration [10]. While SWS dominates during the first part of the night, alternating with only brief periods of REM sleep, REM sleep increases in the second part of the night, then alternating mainly with stage 2 NREM sleep. Stage 1 NREM sleep reflects the transition between wakefulness and sleep and is characterized by low-voltage, mixed-frequency waves in the EEG usually paralleled by slow, rolling eye movements in the EOG. This transitional sleep stage leads to stage 2 NREM sleep, which is identified by the presence of specific EEG patterns known as K complexes and sleep spindles. In the initial sleep cycle, stage 2 NREM sleep is usually followed by SWS, which is characterized by a great proportion of high-voltage slow wave activity in the EEG covering at least 20% of stage 3 and 50% of stage 4 NREM sleep. The ultradian sleep cycle generally ends with REM sleep, which resembles wakefulness due to its desynchronized EEG activity. REM sleep is characterized by low-voltage, mixed-frequency activity in the EEG as well as muscle atonia and episodic bursts of rapid eye movements. Tonic and phasic types of REM sleep can be distinguished, with bursts of rapid eye movements most commonly used as marker of phasic REM sleep activity. The average proportions of sleep stages in healthy young adults are 2–5% for stage 1 NREM sleep, 45–55% for stage 2 NREM sleep, 3–8% for stage 3 NREM sleep, 10–15% for stage 4 NREM sleep, and 20–25% for stage REM sleep.

Sleep is further characterized by changes in cerebral activity across the sleep–wake cycle [11]. At a global level, brain activity decreases from waking to NREM sleep and returns back to waking levels during REM sleep. More specifically, NREM sleep shows reduced relative activity in frontal, parietal, and temporal regions of the heteromodal association cortex as well as in the thalamus compared to waking. In contrast, REM sleep is associated with increased relative activity in the pontine reticular formation as well as in the limbic and paralimbic cortex in comparison to waking and NREM sleep. In addition to changes in cerebral activity patterns, the sleep–wake cycle is also accompanied by profound alterations in neurochemistry [12]. Aminergic, i.e. serotonergic and noradrenergic, as well as cholinergic neuromodulatory subsystems of the brainstem seem to play a crucial role in this context. According to the reciprocal interaction model of sleep cycle control, the pontine aminergic system is activated during waking, thereby inhibiting the pontine cholinergic system. During NREM sleep, aminergic inhibition diminishes and cholinergic excitation starts to increase. At the onset of REM sleep, aminergic inhibition is minimal and cholinergic excitation reaches peak levels. The basic concept of this model is supported by recent findings [13]. Several other neurotransmitter systems seem to interact in the brainstem control of sleep cycles.

Memory systems and memory consolidation

Like sleep, memory is not a unitary system. In fact, there are several different classification schemes for human memory. In the context of sleep-dependent memory consolidation, an important distinction is usually drawn between declarative and non-declarative memory systems [14]. Whereas declarative memories are accessible to conscious recollection, non-declarative memories are unconscious and expressed through performance rather than recollection. Declarative memory is further subdivided into memory for facts (semantic memory) and memory for events (episodic memory). Non-declarative memory comprises procedural learning such as skill and habit learning, priming and perceptual learning, simple classical conditioning, and non-associative learning. Declarative and non-declarative memory relate to different neuroanatomical structures. While declarative memory depends on structures of the medial temporal lobe, especially the hippocampus, and the midline diencephalon, non-declarative memory appears to be less dependent on these structures. Procedural learning is primarily assigned to the striatum, priming and perceptual learning to the neocortex, and non-associative learning to the reflex pathways. Simple classical conditioning mainly depends on the amygdala in cases of emotional responses and on the cerebellum in cases of skeletal responses. According to an alternative classification system, human memory includes four long-term memory systems, i.e. procedural memory, perceptual representation system, semantic memory, and episodic memory [15]. A first integration of previous findings

on sleep-related memory consolidation into this classification system has recently been published [16].

The term memory consolidation traditionally refers to a time-dependent process, in which new memories are slowly converted from an initially fragile state into a lasting form, which is insensitive to disruption [17]. Recent findings suggest that memory consolidation not only stabilizes new memories but may also serve to enhance them [18]. According to this view, a time-dependent stabilization process takes place during wakefulness, which makes memory representations less susceptible to interference. In addition, consolidation-based enhancement takes place during sleep, which allows for additional learning in the absence of further training. While this concept of memory consolidation refers to procedural learning, an alternative model focuses on hippocampus-dependent memory consolidation [19, 20]. According to this model, neocortical–hippocampal information flow during wakefulness takes place in association with theta/gamma oscillations and high levels of acetylcholine. This information flow is reversed during SWS with the occurrence of hippocampal sharp wave bursts and low levels of acetylcholine. During subsequent REM sleep, high levels of acetylcholine suppress further hippocampal feedback to the neocortex and the information flow from the neocortex to the hippocampus is again facilitated. Recent evidence suggests that an already stabilized memory returns to a labile state by reactivation, which allows for further modification, strengthening or even erasure of the memory [21]. To restabilize this memory, a subsequent process of reconsolidation is necessary.

Trajectories of neurocognitive aging

Age-related cognitive decline is characterized by healthy and pathological processes in adult brain development. In this context, an important distinction is drawn between normal aging, mild cognitive impairment (MCI), and Alzheimer's disease (AD) [22]. The concept of MCI was introduced to identify individuals who are at risk of developing AD, in an early stage of cognitive decline, when future therapeutic interventions are expected to show the highest benefits for patients. Today, a diagnosis of definite AD can only be made after post-mortem neuropathological examination of the brain. However, different trajectories of neurocognitive aging can also be distinguished by modern neuroimaging methods [23]. While normal aging is accompanied by changes in the prefrontal cortex and the basal ganglia, MCI and AD are characterized by pronounced changes in the medial temporal lobe region. These changes are associated with executive function deficits in healthy older adults and impaired long-term memory function in patients with MCI and AD. Within the medial temporal lobe region, the entorhinal cortex seems to be particularly affected by atrophy in MCI, whereas hippocampal volume declines are less prominent in this early stage of cognitive decline. In contrast, AD is characterized by severe hippocampal atrophy. Current pharmacological treatment strategies in AD mainly target cholinergic abnormalities within the disease such as alterations in acetylcholine release [24]. These days, acetylcholinesterase inhibitors (AChE-I) are commonly used for the symptomatic treatment of AD.

Even though neurocognitive aging may be associated with dementia and decline, several factors contribute to trajectories of successful aging [25]. In this context, cardiovascular and cognitive training programs, a low-calorie diet, and an active involvement in a social network seem to be of particular importance. Interestingly, functional neuroimaging findings indicate that low-performing older adults recruit a similar network to young adults during a memory task, whereas high-performing older adults engage a different neurocognitive network [26]. This change in brain activity might compensate for age-related neural decline in healthy older adults. While a positive view of aging seems to be justified for the young old, the oldest old do experience more and more limitations of their functional capacity [27]. This is especially evident in cases of dementia. In the Berlin Aging Study, the prevalence rate for moderate to severe dementia increased from 0% in the 70- to 74-year-olds to about 40% in the 90- to 94-year-olds [28]. According to numerous centenarian studies, about 15–25% of centenarians show intact cognitive functioning [29]. There are even centenarians without any evidence of neurodegenerative disease as determined by post-mortem neuropathological examination. Hence, the study of centenarians is of great interest in the current search for the crucial factors that protect against dementia.

The significance of sleep for memory consolidation in old age

The significance of sleep for memory consolidation has been investigated for many years. Although aging affects both sleep and memory, only a few studies have

addressed this topic in the context of aging so far. A first approach was made by reviewing the literature on age-related changes in sleep and memory within the scope of recent findings regarding sleep-related memory consolidation in young adults. The first empirical findings published in this context suggest an impairment of sleep-related memory consolidation in old age. Based on these findings, a putative model of sleep-related memory consolidation in old age was proposed.

The relationship between sleep and memory consolidation in old age

Many findings point to the importance of sleep for the consolidation of newly formed memory traces in young adults, while sleep-related memory processes in older adults remain to be explored in further detail [30]. Previous research in young adults suggests that REM sleep promotes procedural learning processes, whereas SWS facilitates declarative ones [31]. Other findings indicate that an optimal level of procedural memory consolidation is only reached if SWS precedes REM sleep during the course of sleep [32]. With regard to declarative memory, transcranial stimulation of slowly oscillating potentials during early nocturnal NREM sleep was found to increase retention of declarative memories [33]. In addition, stage 2 sleep spindles seem to play an important role in the consolidation of declarative memories [34]. Stage 2 sleep spindles were also shown to be involved in procedural memory consolidation [35]. In contrast to this, the consolidation of emotional memories was found to be associated with REM sleep [36].

It is evident that sleep and memory are commonly affected by general aging processes of the brain [30]. These processes include gray and white matter atrophy, synaptic degeneration, reduced blood flow, and changes in neurochemistry [26]. The commonality in aging trajectories of sleep and memory is reflected, for example, in age-related changes of frontal brain activity patterns both during sleep as well as memory processes [37, 38]. Apart from such commonalities, there may also be interrelationships between the two aging trajectories of sleep and memory. Many sleep parameters of relevance for sleep-related memory processing in young adults decline with age, such as REM sleep and SWS percentages, rapid eye movement, and sleep spindle activity or EEG power in the delta band. These age-related changes in sleep may affect sleep-related memory processing in older adults, leading to impaired daytime memory performance in the aged. In line with this, older adults were found to show less improvement in a perceptual motor skill task from one day to another, compared to middle-aged adults [39]. Age-related increases in daytime napping may partly compensate for this loss of nighttime sleep quality in older adults, as recent findings suggest that napping has the same beneficial effects on learning as a night of sleep [40]. Age-related changes in brain regions involved in memory processing such as the hippocampus may also adversely affect the quality of memory consolidation during sleep in older adults.

In summary, general aging processes of the brain lead to commonalities in aging trajectories of sleep and memory [30]. In addition to that, there may be interrelationships between age-related changes in sleep and memory through mechanisms of memory consolidation during sleep. Changes in sleep characteristics with aging may lead to impaired memory consolidation during sleep, thereby affecting daytime memory performance in older adults. Vice versa, age-related structural and functional changes of brain regions involved in memory processing are expected to reduce efficiency of memory consolidation during sleep in older adults. At present, it is unclear which components are crucial for establishing a link between sleep and memory in late adulthood. Due to the scarcity of empirical findings, it seems worthwhile to investigate the memory promoting effects of sleep in older adults in further detail, thereby diminishing the gap between two research domains on aging with probable advantages for studying both sleep and memory processes in old age.

Figure 5.1 illustrates the main conclusions of this chapter.

Sleep-related memory consolidation in old age: empirical findings

Sleep-related memory consolidation has not been studied extensively in older adults so far. However, there is increasing evidence that sleep-dependent memory consolidation declines with age, even if young and older adults show similar degrees of initial learning [41].

In a recent study, the effects of REM sleep manipulation on declarative and procedural memory consolidation were investigated in healthy older adults [42]. In this study, a first group was deprived of REM sleep

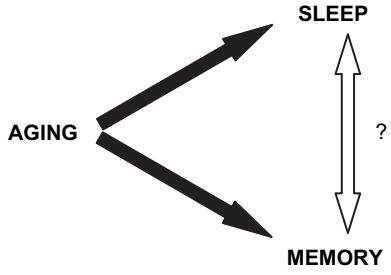

Figure 5.1. Age-related changes in sleep and memory: commonalities and interrelationships. The relationship between the aging trajectories of sleep and memory is characterized by commonalities through general aging processes of the brain (black arrows) and possible interrelationships through mechanisms of sleep-related memory consolidation (white arrow).

by selective REM sleep awakenings, while a second group was woken during stage 2 NREM sleep in equal frequency. Physiological REM sleep augmentation was realized by REM sleep rebound following a night of selective REM sleep deprivation, while pharmacological REM sleep augmentation was accomplished by administering an AChE-I in a double-blind, placebo-controlled design before bedtime. Declarative and procedural memory performance was tested by a paired associate word list and a mirror tracing task the evening before the study night and the morning thereafter. Although selective REM sleep deprivation led to a significant reduction in total and phasic REM sleep duration compared to stage 2 NREM sleep awakenings of equal frequency, declarative and procedural memory consolidation remained unaffected by the sleep manipulation. While both REM sleep augmentation groups showed a significant increase in phasic REM sleep duration compared to the placebo condition, only pharmacological cholinergic REM sleep manipulation exerted a significant positive effect on procedural memory consolidation. The findings of this study suggest that REM sleep does not critically affect procedural memory consolidation in old age, possibly due to age-related changes in cholinergic neurotransmission. Since procedural memory consolidation was improved only after cholinergic stimulation of phasic REM sleep, cholinergic activation seems to be a crucial component of REM sleep-related procedural memory consolidation in old age.

Another recent study investigated the significance of SWS for declarative memory consolidation in middle-aged adults compared to young adults [43]. In this study, declarative memory consolidation was studied during early nocturnal sleep, which is dominated by SWS, as well as during late nocturnal sleep, which is rich in REM sleep. The age groups did not differ with regard to learning performance before sleep. As expected, younger adults showed more SWS during early nocturnal sleep than middle-aged adults. Younger adults also showed superior declarative memory performance after early nocturnal sleep. The amount of SWS during early nocturnal sleep in the middle-aged group was comparable to the amount of SWS during late nocturnal sleep in the young group. Interestingly, the two age groups did not differ with regard to declarative memory performance after the respective sleep periods. Altogether, the findings of this study suggest that sleep-related declarative memory consolidation declines with age. It is of interest that several lines of evidence indicate that the hyperactivity of the hypothalamo-pituitary-adrenal (HPA) axis system in old age has a negative effect on sleep-related declarative memory consolidation in older adults [44].

The effect of age-related changes in stage 2 sleep spindle density has recently been investigated with regard to procedural memory consolidation [45]. The density of stage 2 sleep spindles was investigated in young and older adults before and after learning a simple motor task. In this study, older adults showed similar results with regard to performance improvement and sleep spindle density change when percentage measures of baseline levels were investigated. However, the density of stage 2 sleep spindles was increased after motor learning only in the young group. Moreover, the increase in spindle density was correlated with initial performance level only in young adults. These findings suggest that the association between sleep spindle activity and memory consolidation changes with aging.

A putative model of sleep-related memory consolidation in old age

The findings of our recent study suggest that, by pharmacologically stimulating cholinergic activity in older adults, plasticity-related processes during sleep are facilitated [42]. At first glance, this finding seems to contradict current models of state-dependent stages of memory consolidation, which propose that low levels of acetylcholine are essential for memory consolidation during NREM sleep [20]. However, considering the cholinergic hypothesis of cognitive deficits in aging and AD, cholinergic medication could in fact counteract cholinergic hypofunction in old age,

thereby facilitating processes of memory consolidation [24]. In other words, if the level of cholinergic activation is generally low in old age then the cascade of state-dependent stages of memory consolidation cannot be triggered.

The increase in REM density following cholinergic medication observed in our study could be a crucial component for sleep-related procedural memory processes in old age [42]. It is well known that REM density is reduced in old age [46]. Moreover, phasic activity during REM sleep seems to be essential for plasticity-related processes during sleep [47]. An AChE-I could compensate for the reduction of REM density due to cholinergic hypofunction in old age, thereby allowing for restored procedural memory consolidation during sleep.

It might appear contradictory that, in contrast to procedural memory consolidation, declarative memory consolidation remains unaffected by cholinergic medication in old age [42]. However, aging is associated with a decline in declarative memory performance based on structural and functional changes in the hippocampus and other relevant brain areas [30]. Hence, even though the cascade of state-dependent stages of memory consolidation might be retriggered by an AChE-I in old age, compensating for cholinergic hypofunction, the benefits from these processes could be limited due to functional and structural changes of the brain. It is of interest to note in this context that age-related changes in procedural memory are less pronounced than in declarative memory [48]. Based on the findings of our study, a putative model of the relationship between sleep and memory in old age is illustrated in Figure 5.2.

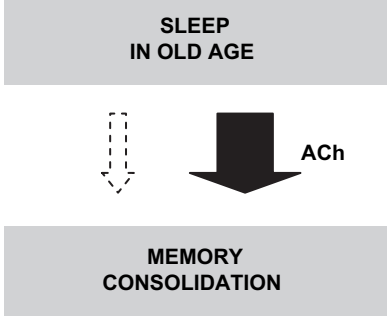

Figure 5.2. The relationship between sleep and memory consolidation in old age: a putative model. In this model, sleep critically affects memory consolidation in old age only if the level of cholinergic activation (ACh) is increased, acting against cholinergic hypofunction.

Outlook

Normal aging is just one research domain where it seems worthwhile to investigate the relationship between sleep and memory in further detail. Several psychiatric disorders such as Alzheimer's disease and depression are associated with disturbances of both sleep and memory [49, 50]. At present, it is unclear to what extent these disturbances are interrelated, as research within the cognitive neuroscience of sleep has only started moving beyond the study of healthy young adults. Without doubt, research with regard to the consolidation of newly formed memory traces during sleep offers a wide field for future studies, which might fundamentally alter the way we view age-related processes of memory decline today.

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Sleep and autonomic dysregulation in the elderly

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The primary function of the autonomic nervous system (ANS) is maintenance of homeostasis controlling involuntary functions of the body such as circulation and heart rate, respiration, thermoregulation, neuroendocrine secretion, and gastrointestinal and genitourinary function. Sleep–wake cycle control and ANS are intimately related on an anatomical, physiological, and neurochemical basis. ANS function state-dependent changes have been well recognized and described. The first to understand the importance of ANS modifications during sleep stages in clinical medicine were Lugaresi and colleagues in the early 1970s who described the dramatic changes in systemic and pulmonary blood pressure (BP) associated with apneas and renewal of breathing in patients with Pickwick's syndrome [1, 2].

Sleep and ANS interactions

The major confirmation of the relationship between sleep and ANS is the presence of dynamic synchronous fluctuations in sleep phases and autonomic functions. Sleep state changes are co-ordinated principally by the pons, basal forebrain areas, and other subcortical structures, and the main neurotransmitters are norepinephrine, serotonin, and acetylcholine. The same neuronal population that produces and distributes these neurotransmitters constitutes the central anatomical substrate of the sympathetic and parasympathetic nervous systems. The central autonomic network, through its ascending and descending connections between the hypothalamic-limbic region and the nucleus tractus solitarius in the medulla, orchestrates the two divisions of the ANS. Sleep induces profound changes in ANS functions and disorders of ANS affect vital functioning during sleep including circulation and respiration. Non-rapid eye movement (NREM) sleep is characterized by electrocortical synchronization, reduced muscle tone, and stable parasympathetic predominance. Breathing and cardiocirculatory monitoring document a progressive deactivation from stage 1 to stage 4 NREM sleep. During light sleep these functions alternate phases of activation and deactivation every 20–40 seconds [3].

All these changes suggest an increased sensitivity of the baroreceptor reflex that contributes to the reduced variability of arterial pressure typical of NREM sleep [4, 5]. In NREM sleep, sympathetic activity may be transiently increased by arousal stimuli, coinciding with the appearance of K complexes in the electroencephalogram. This is associated with increased heart rate and respiration. During NREM sleep respiration is controlled by an automatic system localized in the medulla that is activated by chemical stimuli. Rapid eye movement (REM) sleep instead is characterized by electrocortical desynchronization, muscle atonia, and phasic motor and autonomic changes. Autonomic function during REM sleep is characterized by marked phasic fluctuations of sympathetic and parasympathetic activity and impairment of baroreflex responses and thermoregulation. During tonic REM sleep there is a marked bradycardia and decreased peripheral resistance resulting in a decrease in arterial pressure interrupted by large transient increases in arterial pressure and heart rate during bursts of rapid eye movements and muscle twitches. This is the result of phasic inhibition of parasympathetic activity and phasic increases in sympathetic discharge. Irregularity in breathing is typical of REM sleep and it is caused by the extremely various behaviors of medullary respiratory neurons during this stage. Some studies showed that the central respiratory drive, although erratic, is often increased in REM sleep. It is also known that medullary respiratory activity in REM sleep is influenced by at least one type of phasic REM sleep event, the pontine-geniculate-occipital spikes wave, a finding clearly indicating non-respiratory and state-specific influences on the respiratory system in REM sleep. Nocturnal monitoring of breathing, pulse rate, systemic arterial pressure, and peripheral vasomotor activation discloses autonomic

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deactivation that, appearing at sleep onset, continues into deep sleep. Marked autonomic reactivation characterizes REM sleep. These autonomic patterns broadly fit the idea that NREM sleep corresponds to a deactivation of brain functions, whereas REM sleep is the outcome of an endogenous brain reactivation. However, not all autonomic activities have the same nocturnal trend. Spontaneous sympathetic skin responses (SSRs) are particularly abundant during deep (stages 3 and 4) sleep when breathing and cardiocirculatory systems stabilize at a minimum level of activities and evoked SSRs are markedly inhibited in NREM and REM sleep, despite the fact that breathing and circulation behave differently in these two types of sleep [6].

The study of regional blood flow (and, hence, metabolism and synaptic activities) confirms that the functional state of the brain during sleep is not merely oriented towards activation (REM sleep) or deactivation (NREM sleep). In deep sleep, for example, there are cortical areas (e.g. the hippocampus) and subcortical areas (e.g. the amygdala) that are directly involved in the autonomic expression of emotion, which maintain a flow (and, hence, a functional level) similar to that of wakefulness [7].

The characteristics of thermoregulatory control vary significantly between sleep phases and wakefulness and with time of the day, being modulated by the circadian system and sleep control mechanisms. Body temperature is regulated at a lower level during NREM sleep than during wakefulness, with a decrease in body temperature and metabolism. Thermoregulatory responses to changes in peripheral or core temperature in animal studies show qualitatively different responses in NREM compared to REM sleep. During NREM sleep thermoregulation mechanisms are operative and the ambient thermal load variations are balanced. This homeothermy is controlled by hypothalamic preoptic integrative mechanisms that drive subordinate brainstem and spinal somatic and visceral mechanisms. In contrast, transition from NREM sleep to REM sleep is characterized by disruption of ongoing thermoregulation that is mostly suspended in REM sleep. In this phase there is a marked inhibition of thermoregulation and the changes in body temperature occur passively in relation to the heat environmental load. The result is that the temperature of the body changes according to its thermal inertia [8]. On the other hand, thermal environment and body temperature are important determinants of sleep architecture, having a prominent influence on both the amount and distribution of arousal states. In particular, some studies showed that in a cold environment there is an increase in wake, sleep latency, and movement time and the decrease in sleep time is due mostly to decreased REM sleep and stage 2 of NREM sleep [9]. In humans the sleep–wake cycle has also been related to the rhythm of body core temperature. In addition there are daily cycles with changes in body temperature independent of arousal states; they are under the control of the circadian system, which also influences the organization of vigilance states. In mammals the suprachiasmatic nucleus in the anterior hypothalamus serves as the central neural pacemaker of the circadian timing system. Hormones have a mutually regulatory influence on circadian rhythms and the sleep–wake cycle. Melatonin levels are higher during night sleep; cortisol is low at the usual sleep onset time, but high at the habitual morning wake time. The thyroid stimulating hormone peak in the middle of the night is blunted by sleep; growth hormone, prolactin, and parathyroid hormone show a pronounced sleep-related increase in levels. Renin levels are augmented in stages 3–4 of NREM sleep. Because of this strong anatomical and functional relationship between sleep and ANS functions, sleep disturbance is commonly found in ANS dysfunctions and sleep diseases are often accompanied by modifications in the ANS. A large number of neurological and general medical disorders are associated with failure of the ANS and many of these patients have sleep disturbances (Table 6.1). The prevalence of many of these conditions is increased by aging. Furthermore, many sleep disorders that occur frequently in the elderly are accompanied by ANS dysfunction (Table 6.2).

Sleep in the elderly

Normal human NREM sleep is commonly divided into stages 1 to 4 according to the different EEG findings, with a predominance of slow waves in stages 3–4. REM sleep is characterized by a desynchronized EEG pattern, loss of muscle tone, and motor activity. In adults, sleep normally begins in NREM sleep and progresses through deeper NREM stages (2, 3, and 4) before the first REM sleep episode, approximately 80–100 minutes later. Thereafter, NREM sleep and REM sleep cycle with a period of approximately 90 minutes. NREM stages 3 and 4 concentrate in the early NREM cycles and REM sleep episodes lengthen across the night [10]. Under normal conditions, the circadian rhythm of body temperature parallels the sleep–wake cycle [11]. The temperature curve crests

Table 6.1. Disorders with autonomic failure associated with sleep dysfunction

Neurodegenerative and prion diseases:
Multiple system atrophy (MSA)
Parkinson's disease
Progressive supranuclear palsy (PSP)
Fatal familial insomnia
Cerebellar degeneration
Alzheimer's disease
Central nervous system lesions and other neurological disorders:
Hypothalamic tumors
Brainstem lesions
Stroke
Epilepsy
Multiple sclerosis
Headache
Neuromuscular diseases:
Myasthenia gravis
Myotonic dystrophy
Amyotrophic lateral sclerosis
Peripheral nervous system diseases:
Autonomic neuropathies
General medical disorders:
Cardiac arrhythmias
Myocardial infarction
Diabetes
Bronchial asthma
Chronic renal failure
Chronic fatigue syndrome
AIDS

between 4 pm and 10 pm (the wake maintenance zone) and nadirs between 04:00 and 07:00 (the "sleep propensity zone"). Sleep architecture changes with age with an increased percentage of time spent in stages 1 and 2, and a reduction in sleep spindles and in the percentage of time spent in stages 3–4 (slow wave sleep). Time spent in REM sleep shows a small decrease from middle to old age with a phase advancement towards the early part of the night and the inability to phase shift readily. Total sleep time, total time in bed, sleep onset latency, wakefulness after sleep onset, and daytime naps increase with age [12] with a decline in sleep efficiency from 86% around 45 years to about 79% in people older than 70 years [13]. Increased periods of wakefulness during the night sleep and reduced sleep consolidation and stability with brief arousals are common and occur at rates of about 15/hour in elderly individuals without breathing/sleep disorders. Older people sleep less during the circadian propensity zone. This causes increased nocturnal and early morning awakenings and augmented sleepiness during the wake maintenance zone. These changes are parallel to the age-related phase advance in the temperature rhythm [11]. Aging is associated with desynchronization of circadian rhythms with a reduction of amplitude of the body core temperature oscillation [12] and with altered secretion of several hormones (growth hormone, melatonin, cortisol and interleukin-6) [14].

Table 6.2. Sleep disorders associated with autonomic dysfunction

Obstructive sleep apnea syndrome (OSAS)
REM behavior disorder (RBD)
Restless legs syndrome (RLS)
Periodic limb movements (PLMs)

Sleep disorders are more common in advanced age than in young people. The prevalence of insomnia (46% >65 years), obstructive sleep apnea syndrome (OSAS) (30% >65 years), REM behavior disorder (RBD) (with a typical onset after the sixth decade), restless leg syndrome (RLS) (10% >65 years), and periodic limb movements (PLMs) (34%) increases with aging [11]. The increased prevalence of sleep disorders with aging may be influenced by medical co-morbidities and medications that alter sleep architecture.

Autonomic nervous system in the elderly

The effect of aging on ANS function is complex and heterogeneous: not all parts of the ANS are involved in the same way and at the same time. Sympathetic or parasympathetic systems may be involved to a different extent and even within the same system the dysfunction may be extremely varied. Age-related changes in ANS function are linked to changes in body composition, neuronal loss, neurotransmitter underproduction or reduced receptor function, tissue damage (primarily cardiac and vascular), and hormonal changes. Neuropathological studies on humans and animals demonstrated an age-related neuroaxonal dystrophy involving sympathetic intraganglionic terminal axons and synapses [15]. It is well accepted that plasma supine norepinephrine increases with age [16]. Moreover, the elderly often present with co-morbidities and concomitant medications that by themselves may influence autonomic function. Many studies have shown that other variables such as physical activity, gender, environment, and alimentation also have a fundamental role in the development of an age-linked autonomic dysfunction. The evaluation of age-dependent alterations of the ANS is not simple and within the literature it is hard to find complete agreement on this topic. This may be due to the methodological differences among studies, which are often conducted on animal models with intrinsic difficulties in extrapolation to humans, and to other age-unrelated variables, which are often not considered. The different domains of the ANS are involved to a different extent in age-related autonomic dysregulation.

Blood pressure

Age is related to structural changes in the cardiovascular system and its neuro-hormonal control that may compromise blood pressure (BP) homeostasis. Chronic and acute BP regulation is due to various local, humoral, and neural factors. Neural regulation of BP occurs via tonic and reflex modulation of both sympathetic and parasympathetic nervous systems. The primary device by which BP is rapidly and reflexively modulated in humans is through the baroreflex mechanism, which maintains circulatory homeostasis by means of negative feedback (Figure 6.1). The baroreflex loop originates at the level of the baroreceptors, which are highly specialized stretch-sensitive nerve endings localized in various regions of the cardiovascular system (carotid artery, aorta, cardiopulmonary region). Stimulation of the baroreceptors provokes activation of specific brainstem regions by means of afferent branches. In response to increasing firing rate of the baroreceptors, efferent sympathetic outflow is inhibited with reduction of vascular resistance, cardiac chronotropy and inotropy, and augmentation of parasympathetic tone with subsequent reduction of cardiac chronotropy. Aging is associated with a specific and selective impairment in baroreflex function with a subsequent decreased ability to alter cardiac period in response to acute alterations in BP and a decreased ability of the baroreflexes to buffer changes in systemic BP [17, 18, 19]. Alterations may occur at different levels of the loop with subsequent baroreflex dysfunction: in the afferent arm (augmented vascular stiffness), in central processing (efferent coupling and its modulators), and in the efferent arm (such as sinoatrial node responsiveness to acetylcholine). The cardiac arm of the baroreflex involves prolongation or shortening of

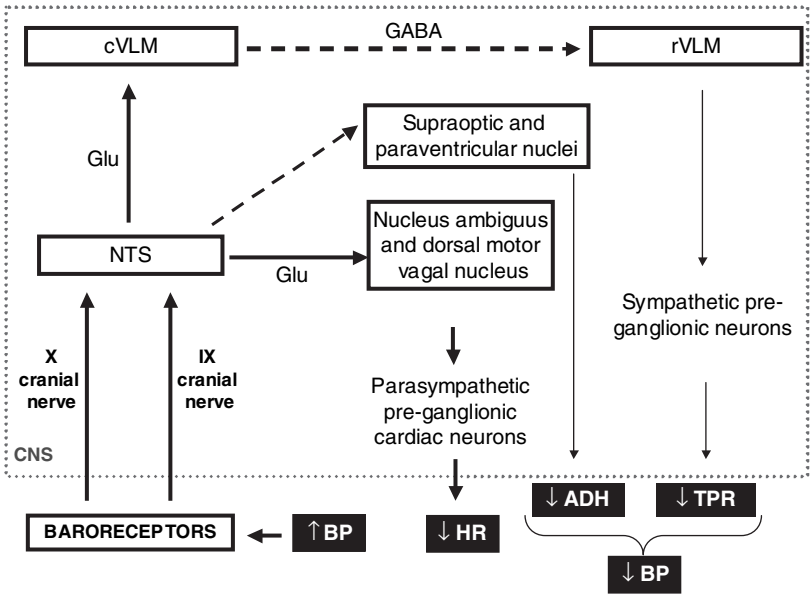

Figure 6.1. Baroreflex loop. NTS, nucleus tractus solitarius; c-rVLM, caudal and rostral regions of the medullary ventrolateral portion; CNS, central nervous system; BP, blood pressure; HR, heart rate; ADH, antidiuretic hormone; TPR, total peripheral resistance; Glu, glutamate; GABA, γ-aminobutyric acid.

the cardiac period in response to changes in baroreceptor input. If examined over a wide range of BPs, there is a sigmoid relation between cardiac period and BP. The linear portion of this stimulus–response curve is used to quantify cardiovagal reflex sensitivity (BRS). Advancing age is related to a decreased cardiovagal BRS and to an increased risk of sudden cardiac death [17]. Changes in baroreflex function with age are associated with functional changes in BP control, which include increased levels of BP variability, augmented BP falls during acute central hypovolemic stress, and possible greater incidence of hypotension during application of physiological stressors. A comprehensive assessment of BP control impairment requires a detailed history focused on medications, volume losses, medical co-morbidity and other signs of autonomic dysfunction, physical examination including measurement of BP and heart rate (HR), also after various stimuli (primarily standing and eating), neurological examination, and laboratory tests including hemoglobin, hematocrit and electrolytes. Autonomic function testing may be very helpful to evaluate the extent of autonomic involvement and to monitor the course of the disorder and the response to therapy. The main clinical presentations of this impaired control of BP are higher levels of supine BP, orthostatic hypotension (OH), and post-prandial hypotension (PPH); these variables are well-recognized risk factors of mortality and morbidity in the elderly population [20].

Orthostatic hypotension is defined as a reduction in systolic BP of at least 20 mmHg or diastolic BP of at least 10 mmHg within 3 minutes of assuming an erect posture [21]. Prevalence of OH increases with age: it is approximately 20% in subjects above 65 years, 30% over 75 years, and 50% or more in frail individuals living in nursing homes [22]. Compared to young people, aged people present with a blunted increment in HR and diastolic BP [16]. An increased prevalence of OH is due to an age-related increase in supine BP and impairment of the physiological mechanisms of maintenance of BP while standing, such as baroreflex sensitivity, adrenergic vasoconstrictor response to sympathetic stimuli, parasympathetic activity, renal activity and blood volume, skeletal muscle pump, vascular elasticity, and left ventricular diastolic filling. The influence of concomitant medications, co-morbidity, and physical activity on OH has been well established (Table 6.3). The most common clinical features of OH are represented by dizziness, lightheadness, weakness, syncope, nausea, paracervical or low back pain, angina pectoris, visual changes, confusion, and impaired cognition; even if dramatic, OH may be asymptomatic. In many older people OH may become symptomatic only after stress such as bedrest for some days, volume depletion, and co-existing illness with pyrexia or diarrhea [16].

The evaluation of a possible OH in the elderly is fundamental for the possible consequences such as falls, syncope, and myocardial infarction. Therapeutic

Table 6.3. Main causes of orthostatic hypotension(OH) in the elderly

Age-related causes of OH	Secondary causes of OH
Reduced baroreflex sensitivity	Medical co-morbidities
Reduced vasoconstrictor response	Volume depletion
Reduced parasympathetic activity	Medications
Reduced renal activity	Bedrest
Increased vascular stiffness	
Reduced left ventricular diastolic filling	

options are non-pharmacological and pharmacological. The former consists of slow changes of posture, avoidance of prolonged standing in hot ambient temperature, raising the head of the bed 10–20 degrees (head-up tilt), elastic waist-high stocking, increased intake of salt and water, physical exercise (primarily swimming). Pharmacological treatments are represented by fludrocortisone, midodrine, and erythropoietine.

Post-prandial hypotension may be defined as a reduction of at least 20 mmHg of systolic BP 1 hour after a meal while sitting [20]. The mechanism of PPH development is complex and not completely understood. Adequate compensation after meal-induced splanchnic pooling requires a precise interaction of ANS, cardiovascular system, and vasoactive gastrointestinal peptides. The impairment of one or most of these levels may lead to PPH [20]. Non-pharmacological treatment of PPH is represented by reduction of alcohol and carbohydrate-rich meals. The somatostatin analog octreotide may also prevent PPH by reducing the release of some gut peptides. Acarbose, an α-glucosidase inhibitor that decreases glucose absorption in the small intestine, attenuates PPH [23]. The coexistence of supine hypertension must always be considered to guide the therapeutic approach.

Heart rate

Control of HR is due to the interaction between sympathetic and parasympathetic systems even if the latter predominates in humans under resting conditions. Intrinsic HR, which represents HR after sympathetic and parasympathetic blockade, decreases with aging [16]. Variability of HR (HRV) has been categorized into high-frequency (HF), low-frequency (LF), and very-low-frequency (VLF) power ranges according to its frequency. High frequency is considered to represent vagal control of HR; LF is jointly contributed by both parasympathetic and sympathetic nerves together with the baroreflex mechanism. The ratio LF/HF is considered to reflect sympatovagal balance or the sympathetic modulation of HR. Heart rate variability has been proposed as a non-invasive tool to predict increased risk for cardiac mortality [24]. Many studies unequivocally demonstrated a decrease of HRV with normal aging [24] in a log-linear manner [16]. Vagal control of HR, assessed by analysis of specific HRV parameters, provides important information about the functioning of the cardiac ANS. Vagal control of HR decreases with advancing age and is generally lower among women [25, 26]. Other variables (ischemic heart disease, exercise capacity, and glucose intolerance) can influence HRV and may confound the assessment in the elderly.

Thermoregulation and sweating

Aging is a recognized factor of impaired thermoregulatory control and it represents the reason why elderly are commonly more exposed to heat and cold stress than younger people. The effect of age on sudomotor pathway and control of core temperature is complex and involves different levels of ANS. First the number of eccrine glands decreases with age because no new units are generated after birth; the consequence is a decline in the number and the density of sweat glands with aging. Moreover, glandular functioning is impaired by the loss of efferent nerve fibers and reduction of skin microvasculature with subsequent hypoperfusion and fibrosis of the periglandular areas. All these alterations lead to a higher thermoceptor threshold, with topographic and gender differences.

Several studies have suggested that baseline body core temperature (BcT) decreases with aging with great variability, although a study conducted by Fox *et al*. in 1972 found no differences between younger and older subjects eliminating confounding factors such as medications, concomitant diseases, and nutrition [27]. Aging can also reduce the circadian amplitude of BcT. The physiological maintenance of body

temperature involves different mechanisms such as heat loss (with increased peripheral blood flow) and heat production (with increased metabolic rate mediated by shivering and non-shivering thermogenesis).

Both mechanisms may be involved during aging with reduced autonomic peripheral response, reduced total body oxygen consumption (reflecting thermogenesis), and reduced subjective sensory thermal perception to cold stress compared to younger controls [28]. Some studies showed that in women the maintenance of BcT is less impaired than in men [27]. Aging is associated with an impaired vasomotor response to temperature changes in both acral and non-acral skin [29, 30]. This could be explained by a reduced skin sympathetic nerve activity [31] and cutaneous vasoconstrictor response to norepinephrine [32]. An impaired control of heat loss during cooling in aged subjects has been reported [33]. Recently De Groot and Kenney [34] assessed the response in anthropometrically matched young and older subjects to mild cold stress, measured by esophageal temperature (i.e. core temperature), skin temperature (i.e. shell temperature), O_2 consumption, and skin blood flow. They found an attenuated skin vasoconstrictor response to mild cold stress and a lack of maintenance of esophageal temperature in older subjects. It is well known that the distal parts of the body may be the more important heat loss effectors of the shell. These results may lead to the conclusion that aged subjects fail in preventing heat loss from the arteriovenous-rich extremities. Thermogenesis is also impaired in elderly primarily because of the loss of active muscle mass [27]. The blunted responses to heat stress in elderly subjects are due to reduced sweat gland output, reduced skin blood flow, a smaller increase in cardiac output, and reduced redistribution of blood flow from renal and splanchnic circulation [27]. Animal studies suggest the possibility that older subjects can compensate for the autonomic thermoregulatory impairment with behavioral thermoregulation [33].

Gastrointestinal function

The functioning of the gastrointestinal (GI) tract is due to hormonal, local, and nervous mechanisms. The GI tract has double innervation: intrinsic neurons belonging to the enteric nervous system (ENS) and extrinsic sympathetic, parasympathetic, and sensory neurons.

Nervous control of the GI tract is primarily due to ENS. Enteric neurons are located within glial cells in small ganglia linked by nerve fiber bundles along the length of the GI tract. This system is organized into two main parts: the myenteric plexus, lying within smooth muscle layers of the gut wall; and the submucous plexus, lying within the connective tissue that separates the mucosa and the smooth muscle layers. Aging is associated with various GI disorders with an increased incidence of motility-related problems often worsened by concomitant diseases or medications. The causes of GI dysfunction in the elderly have not been completely elucidated but the loss or the dysfunction of the neural mechanism of the gut is a possible explanation. ENS and extrinsic gut innervation are affected by age to different degrees. Experimental animal models show age-related damage of enteric neurons both in the myenteric and submucous plexuses where loss of cholinergic neurons and dysfunction of nitrergic neurons (i.e. neurons "using nitric oxide synthesized by nitric oxide synthetase") have been demonstrated [35]. Enteric glia and sympathetic innervation deteriorate with age.

Defects in swallowing and fecal evacuation result in the most severe disability in advanced age [36]. Difficulty in swallowing is one of the most common complaints in the elderly and frequently leads to malnutrition. The most common cause of dysphagia is represented by oropharyngeal disorders due to tongue, pharynx, and upper esophageal sphincter (UES) dysfunction. There is a prolongation of the oropharyngeal phase and a delay in the opening of the UES with an increased volume necessary to induce pharyngeal swallow [37]. Esophageal abnormalities, represented by a small increase of amplitude in the distal part of the esophagus and by a higher pressure needed to produce secondary peristalsis, are very common in elderly subjects. Gastroesophageal reflux disease is another common GI complaint in the elderly and its increased incidence with aging may be caused by changes in lower esophageal sphincter function. The increase in intestinal transit time found in the elderly is mostly due to an increased colic transit time [37]. This functional change is associated with an increased diameter of the colon and a decreased in vitro response to cholinergic and electrical stimulation. The marked increase in fecal incontinence with age is related to a lower mean basal and squeeze anal pressure [37]. Physiological age-related anorexia is another important cause of morbidity in the elderly and the causes are varied. Alterations in taste and smell, in fundal compliance, in secretion of gastrointestinal hormones, in ANS feedback to the central nervous system (CNS),

in leptin and steroid hormones, and in CNS responses to food intake are the main causes of this disorder.

Genitourinary function

The physiological function of the urinary bladder is urine storage and expulsion of urine at the appropriate time. The sympathetic nervous system has a tonic inhibitory influence on the bladder and a stimulatory influence on the urethra to facilitate urine storage by means of the α-adrenergic receptors of bladder and urethra, and by means of β-adrenergic receptors of the bladder body.

The micturition reflex is primarily due to activation of the cholinergic (muscarinic) pathway to the detrusor. Aging is related to various degrees of urinary function impairment due to morphological and functional changes in urine production, delivery, storage, and expulsion. The anatomical basis of age-related urinary dysfunction includes deterioration of detrusor muscle function, bladder wall fibrosis, and increased sensitivity to norepinephrine leading to the manifestation of detrusor overactivity and impaired contractility [38]. Experimental studies demonstrated a reduction in the number of intramural bladder plexus neurons in aged guinea-pigs [39]. Lower urinary tract symptoms increase with age, especially those related to overactive bladder syndrome. They are mostly due to reduced bladder capacity, contraction inhibition, urinary flow rate, urethral pressure profile, and increased post-void residual urine volume.

Urinary dysfunction is the most common complaint in the geriatric population, particularly among those admitted to nursing homes, and incontinence represents the predominant symptom occurring in up to 30% of community-dwelling and 50% of institutionalized elderly subjects [40]. The assessment of urinary dysfunction is an important challenge for clinicians because of the impact on quality of life and the co-existence of various factors influencing urinary activity. Cognitive and motor function, co-morbidity with urological or non-urological conditions (diabetes, sleep apnea, congestive heart failure), and medications (diuretics, calcium blockers, opiates, anticholinergics) may produce or worsen urinary dysfunction [41]. In the aging detrusor there is a slight widening of the spaces between the smooth muscle cells and alterations of sarcolemma within muscle cells. While detrusor overactivity is a significant finding, it does not necessarily include incontinence and 42% of continent healthy women older than 65 years show detrusor overactivity in urodynamic testing [41]. The main symptoms of overactive bladder are represented by frequency and urgency in voiding, with or without incontinence, and are very common in both men and women. Etiology is multifactorial including the age-related anatomical and functional changes in bladder function and multiple conditions affecting the lower urinary tract such as cerebrovascular accidents, bladder obstructions secondary to benign prostatic hypertrophy in men, detrusor instability, and stress in women [40]. Pfisterer *et al.* clinically and urodynamically evaluated 85 community-dwelling women (age 22–90 years; mean 54 years), with and without symptoms suggestive for detrusor overactivity [42]. They found an age-related reduction in maximum urethral closure pressure, detrusor contraction strength, and urine flow rate regardless of the presence of detrusor overactivity. Bladder capacity was slightly reduced in subjects with detrusor overactivity. Older people also may experience impaired bladder contractility with decreased urinary flow rates and increased post-voidal residual. In frail older persons the bladder may also be overactive with weak contractions [41].

Age-related urethral changes are also seen in older people leading to a decreased urethral closure pressure and urogenital atrophy. Nocturia is another common finding in the geriatric population with 90% of individuals by the age of 80 years experiencing this condition [41]. Etiology is multifactorial and includes nocturnal polyuria, primary sleep disorders, and lower urinary tract dysfunction. Older persons have a delay from time of fluid intake to urine excretion; this may be due to higher nocturnal atrial natriuretic peptide and/or altered secretion of vasopressin.

Sexual dysfunction is a common complaint in the elderly: a recent population study evidenced that a decline in sexual function becomes more pronounced with aging [43]. Declines in sexual activity and desire have been reported in numerous studies and have been reported to be more severe in women than men [44]. The human sexual response cycle, defined by Masters and Johnson [45], deteriorates with age. During the excitement phase, scrotal vasocongestion and testicular elevation are reduced and erection is delayed in males. In women, vaginal blood flow and genital engorgement is less than in younger individuals. The plateau phase is prolonged and the pre-ejaculatory secretion is decreased, and lubrification is diminished, uterine elevation is less, and the labia majora do not elevate to the same degree as in younger subjects.

Orgasm is of shorter duration in older males, with fewer and less forceful prostatic and urethral secretions, and the force of ejaculation is reduced. Women retain multiorgasmic capacity but weaker and fewer contractions occur. Resolution results in more rapid loss of vasocongestion. Medications, erectile dysfunction and dyspareunia, psychiatric co-morbidity, psychosocial factors, and alteration in hormones are possible causes of sexual dysfunction in the elderly [44].

Erectile dysfunction is self-reported by almost 1 in 5 men and it increases with age [46]; diabetes, hypertension, obesity, and smoking are additional risk factors. The Massachusetts Male Aging Study found that 52% of men aged 40–70 years had some degree of erectile dysfunction ranging from 39% in men aged 40 years to 67% in those aged 70 years [47].

Lower urinary tract symptoms and sexual dysfunction are highly prevalent in aged men and compromise their quality of life. There is a strong relationship between lower urinary tract symptoms and sexual dysfunction and the link between this is still not clear [48]. In particular increased sympathetic activity is associated with lower urinary tract symptoms secondary to benign prostatic hypertrophy and it has been hypothesized that norepinephrine and α-adrenoceptors constitute the common link because they mediate adrenergic contractions of smooth muscles in the prostate, the bladder neck, the urethra, and the corpus cavernosum [48].

Pupillary function

Pupil diameter and reactivity to different stimuli is regulated by the ANS, which controls the smooth muscle of the iris. Pupil diameter is smaller in infancy, widens progressively until adolescence, and becomes narrower in old age [49]. The magnitude of pupillary responses follows the size with most active pupillary changes in youth. A reduced dark adaptation of pupils is common in elderly people and is probably due to sympathetic impairment [16].

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Part 1
Chapter 7

Sleep and normal aging

Age-related changes in the pharyngeal structure and function in sleep apnea and normal subjects

Giora Pillar, David P. White, and Atul Malhotra

Introduction

Sleep apnea syndrome is a disorder characterized by repetitive cessations of breathing during sleep. Apnea can be central (in which there is no respiratory effort) or obstructive (where effort to breathe continues but there is reduced airflow due to airway obstruction). Although both types of apnea may be affected by age, this chapter focuses primarily on obstructive sleep apnea (OSA), the more common disorder. The physiological consequences of apnea are a rise in $PaCO_2$, a fall in PaO_2, and an increased ventilatory effort against an occluded airway. Ultimately, transient arousals from sleep generally occur, which re-establish airway patency and ventilation. The individual subsequently returns to sleep and the cycle repeats throughout the night.

Clinical symptoms of OSA may consist of loud snoring, daytime sleepiness, morning headache, dry mouth upon awakening, nocturia, fragmented sleep, night sweating, heartburn, and impotence in males. During recent years, extensive research has led to the realization that OSA is a major public health problem, with a large impact on healthcare utilization, increased morbidity (predominantly cardiovascular disorders), and possibly mortality. Both sleep apnea per se and its consequences may change over time, emphasizing the importance of patient age during clinical evaluation.

From a pathophysiological point of view, the principal abnormality in the individual with OSA is an anatomically small pharyngeal airway. During wakefulness, the individual compensates for the deficient anatomy via reflexive increases in the activity of upper airway muscles that maintain airway patency. However, with sleep onset, these protective compensatory reflexes are lost and airway collapse occurs. Both pharyngeal anatomy and physiology may change with age, resulting in the observed age-related increases in the prevalence of OSA [1].

Epidemiology

Classically, OSA is defined as a combination of a complaint of daytime somnolence and a laboratory finding of a respiratory disturbance index (RDI) above 5 events per hour of sleep. When this definition is considered, the prevalence of OSA syndrome is 2–3% and 4–5% in middle-aged women and men, respectively. The prevalence is similar in various geographical regions, and may be somewhat higher in some specific ethnic groups such as Asian Indians, Hispanics, and African-American populations. Whether the increased prevalence in some specific ethnic groups results from direct genetic causes or from ethnic-related characteristics of body phenotype such as upper airway structure or obesity [2] remains unclear. Recently, several community-based studies have been performed to assess the prevalence and impact of sleep disordered breathing on general health. In the Sleep Heart Health Study (SHHS), a large-scale study that longitudinally assesses sleep in community-dwelling adults to study the cardiovascular consequences of sleep disordered breathing (SDB), over 10% of the general population has some degree of SDB, with daytime somnolence correlated with the severity of breathing abnormality [3]. Furthermore, in a survey of over 15 000 individuals, which has been performed as a part of the SHHS, it has been estimated that although the prevalence of OSA is over 4%, only 1.6% had such a diagnosis by their physician, and only 0.6% were actually treated for OSA, indicating under-diagnosis and under-recognition of this important disorder [4]. In the pediatric population, OSA is estimated to occur in 1–3% of children with a peak age of 2–5 years [5], but even higher prevalences have been reported, depending on the diagnostic criteria used. The prevalence of OSA is higher in certain groups, such as those with male gender, genetic factors, hormonal disorders (e.g. hypothyroidism), acromegaly, polycystic ovary syndrome, and specific diseases such as renal failure or diabetes. The prevalence of OSA among obese

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individuals has been reported to exceed 30% [6, 7], and may reach as high as 50–98% in the morbidly obese population [8, 9]. This finding further emphasizes the importance of the interaction of aging and weight; with increasing age especially beyond 65 years, weight and BMI tend to decrease [10]. The overall prevalence of OSA in the elderly is estimated at roughly 30% [11].

Aging has been reported to be a major factor affecting the risk of OSA, with an increased prevalence from 2% to 5% in middle-aged individuals, to 5–8% in patients aged 50–60 years, and higher again in the elderly [12]. Kripke *et al.* reported that age was the second most important predictor of SDB (following obesity) in a population-based survey of over 350 people [13]. Ancoli-Israel *et al.* found that 81% of elderly individuals in a community-based sample had an RDI >5/hour, and 44% had an RDI >20/hour [14]. In a separate study, the reported overall prevalence of OSA in a sample of 358 randomly selected elderly volunteers, as diagnosed by home monitoring, was 17% [11]. Many epidemiologically based studies have noted the age-related increase in RDI [15, 16], and in women, the menopause also represents a major OSA risk factor. In the extremes of aging, some data suggest a survivor effect, such that apnea prevalence may decrease among elderly patients. This is presumed to reflect death of apnea patients from the associated co-morbidities prior to reaching the elderly age groups [17], although this explanation remains quite speculative. The exact reason for the aging predisposition to OSA has not been fully elucidated, but various anatomical and physiological changes with aging will be discussed [1, 18].

OSA phenotypes

The current view of sleep apnea pathogenesis is predicated on the concept that not all individuals get OSA for the same reason. That is, there are a number of underlying pathophysiological variables (anatomy, upper airway muscle function, and central ventilatory instability) that may be important in determining apnea status. In some patients, they may have primarily an anatomical problem, whereas other OSA patients may have primarily a problem with upper airway muscle dysfunction. Thus, some investigators have suggested a variety of sleep apnea phenotypes whereby a particular variable (or group of variables) increases the risk of (or protects from) the development of OSA. These phenotypic clusters are potentially important since therapies targeting the underlying pathogenesis of the condition are likely to be different for each of these subgroups. For example, if an agent were available to increase pharyngeal dilator muscle activity, such an agent would be likely to benefit primarily those with dysfunctional upper airway muscles. On the other hand, such an agent might be predicted to have deleterious effects in patients with unstable ventilatory control as the primary pathophysiological abnormality. Thus, a thorough understanding of OSA pathogenesis requires consideration of these different pathophysiological clusters. Moreover, the abnormalities or group of abnormalities contributing to OSA in the elderly remain unclear (see Figure 7.1).

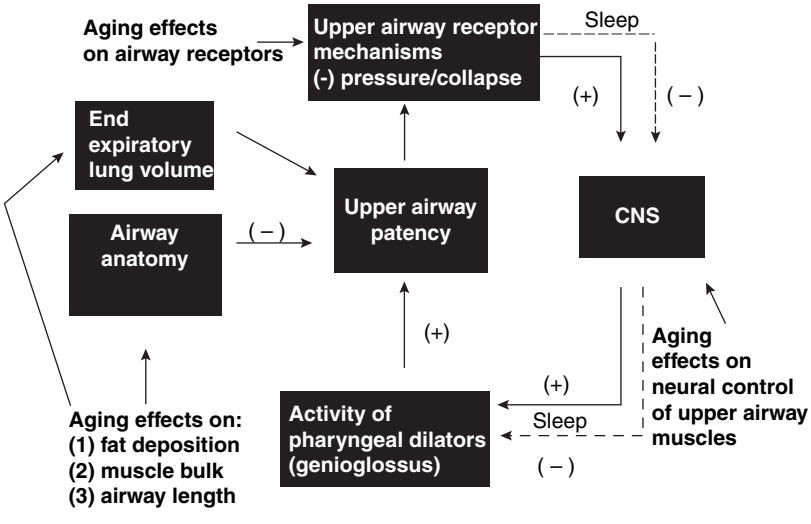

Figure 7.1. The pathogenesis of OSA and how it may be affected by aging. Starting with airway anatomy, this can have deleterious effects on upper airway patency. Through upper airway receptor mechanisms during wakefulness, there is an increase in the activity of the pharyngeal dilator muscles. However, during sleep, these protective mechanisms fail leading to a fall in activity of the pharyngeal dilator muscles and an increased propensity for loss of upper airway patency. Aging may compromise upper airway anatomy, and/or neural control of upper airway muscles either through the CNS or through peripheral upper airway receptor mechanisms. Finally increased end expiratory lung volume can promote upper airway patency, although this mechanism could also be compromised with aging.

The role of the upper airway (UAW)

The upper airway requires stiffness of the soft tissue walls around it and activity of the dilator muscles to maintain patency. Any reduction in UAW cross-sectional area, change in its length, muscle activity, or a combination of these variables, may lead to vulnerability of the UAW to collapse. Many of these characteristics may be affected by aging.

UAW anatomy

Generally, the UAW may be divided into parts: the nasopharynx (velopharynx, behind the soft palate), the oropharynx (behind the tongue), and the hypopharynx (just above the epiglottis, see Figure 7.2).

In the transition from wakefulness to sleep, both healthy subjects and OSA patients experience some degree of dilator muscle relaxation and narrowing of the UAW. Thus, when UAW is anatomically small during wakefulness (as is the case in OSA), the risk for pharyngeal collapse is increased. Indeed, many studies have demonstrated a small pharyngeal airway in apnea patients compared to controls, with the smallest airway luminal size generally occurring at the level of the velopharynx in both patients and controls [19]. However, most of these studies have been performed in subjects during wakefulness, when anatomical investigation reflects an interaction between anatomy and muscle activation and not pure anatomy. Isono *et al*. have extensively studied airway anatomy during general anesthesia (with complete neuromuscular paralysis) [20]. The authors have reported a positive closing pressure (Pclose) in patients with OSA, meaning that the airway was collapsed at atmospheric pressure and required positive pressure to reopen [20]. Normal controls, on the other hand, had patent airways at atmospheric pressure and required suction (negative pressure) to collapse the pharynx. This observation strongly supports the existence of a biomechanical (anatomical) abnormality of the upper airway in apnea patients. In addition, the authors showed a strong correlation between Pclose and the oxygen desaturation index indicating a clear relationship between airway anatomy and apnea severity, although considerable variance was observed in this relationship. Endoscopic evaluation also demonstrated a larger cross-sectional area of the velopharynx in controls compared to OSA patients, again suggesting deficient anatomy in the apnea patients [20]. One possible limitation of this otherwise unique and persuasive study is the potential development of atelectasis and reduced lung volume under conditions of general anesthesia, hyperoxia, and airway suctioning. Lung volume can have a substantial influence on upper airway size and RDI in apneics [21, 22]; therefore the changes in lung volume in the Isono study could have influenced the reported results.

The soft tissues surrounding the upper airway may also have an independent role in vulnerability to collapse. Sleep apnea patients have increased thickness of the lateral pharyngeal walls [23]. This finding is helpful in explaining the reduced lateral diameter of the airway lumen in OSA patients as compared to controls. No important skeletal differences were observed in these studies, implicating soft tissues as the major anatomical difference between apneics and controls. Schwab *et al*. have argued therefore that lateral wall thickening and ultimately collapse are important components in the pathogenesis of OSA in adults [24].

In order to investigate the potential changes in UAW dimensions that may contribute to the age-related increase in OSA prevalence, several imaging studies have been performed. Martin *et al*. [25] used acoustic reflection in 60 men and 54 women with an

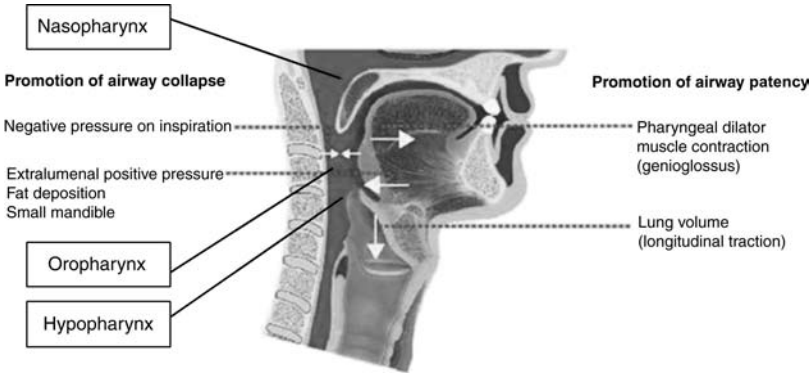

Figure 7.2. Inspiratory negative pressure, anatomically narrow airway, and extraluminal positive pressure tend to promote pharyngeal collapse. Upper airway dilator muscle and increased lung volume tend to maintain pharyngeal patency. (Modified from Malhotra A, White DP. Obstructive sleep apnea. *Lancet* 2002;**360**:237–45.)

age range of 16–74 years. The authors found that all upper airway dimensions, except at the oropharyngeal junction, decreased with increasing age in both healthy men and women ($r > -0.24$, $p \leq 0.05$). However, Mayer *et al.* [26] reported that older patients (>63 years) had larger upper airways at all pharyngeal levels than the youngest group of patients (<52 years), using a CT assessment of airway size. Similarly, Burger *et al.* [27] reported an increase in pharyngeal airway lumen size with aging at FRC (73 vs. 49 mm^2); however, only normal subjects were included potentially leading to issues from survivor effects and selection bias. We have also recently studied the age-related anatomical and pathophysiological mechanisms that potentially predispose to pharyngeal collapse in older individuals [1]. Upper airway anatomy was investigated in 38 subjects using volumetric analyses of magnetic resonance images in order to quantitatively assess the structures of interest. Anatomical changes associated with aging included increased parapharyngeal fat pad size ($R = 0.59$; $p = 0.001$), and changes in airway length (see below). Johnston and Richardson [28] studied 16 young adults (mean age 20 years) using cephalometric films and re-studied them after 32 years. The authors reported an age-related tendency towards a longer and thicker soft palate, and narrower oropharynx [28].

Thus, some imaging data suggest that the airway lumen size may be reduced with aging, potentially increasing the vulnerability to collapse, although this observation is quite variable across studies. The studies assessing the effects of age on airway anatomy are too sparse and disparate to draw firm conclusions.

UAW length

The potential importance of UAW length has been raised as a factor in the pathogenesis of OSA, initially in relation to the male gender predisposition to pharyngeal collapse and later in relation to age-dependent changes. We studied the gender-related differences in UAW collapsibility in normal healthy non-obese young adults, and found that males had increased UAW collapsibility in response to inspiratory resistive loading, despite similar central respiratory drive (ventilatory response to load) and similar UAW dilator muscle activation (genioglossus and tensor palatini) [29]. Therefore, we concluded that there was a fundamental gender-related difference in UAW anatomy and/or tissue characteristics. Since cross-sectional UAW is generally greater in men than women, intrinsic pharyngeal size is an unlikely explanation for the male predisposition to pharyngeal collapse. However, in a subsequent study we found that men had a substantially and significantly longer UAW than women, independent of body size [30]. Using finite element modelling, we further demonstrated a major independent effect of pharyngeal airway length on upper airway collapsibility. As non-rigid tubes become longer they are increasingly prone to collapse (assuming similar tethering); we concluded that airway length is a potentially important mechanism responsible for the increased UAW collapsibility. In a subsequent study, we recently reported that pharyngeal airway length correlated significantly with aging in women ($R = 0.56$, $p = 0.007$), but not in men ($R = 0.18$, $p = 0.47$), and argued it may be important in the age-related increase in OSA, at least in women [1]. This claim is supported by a subsequent study on 24 patients with OSA. We found a significant positive correlation of $r = 0.41$ between RDI and UAW length, which persisted when UAW length was normalized to body height ($r = 0.42$). Interestingly, airway length may also partially explain the age-related change in the gender predisposition of OSA in children. While in pre-pubertal children the prevalence of OSA is similar between genders, there is a known male predominance in the post-pubertal population and in adults. Studying UAW length of pre- and post-pubertal males and females, we recently observed that in pre-pubertal children UAW length was similar between boys and girls, and even shorter in boys when normalized to body height. However, the pharyngeal airway became significantly longer in post-pubertal males compared to females (both absolute length and length normalized to body height). We argued that the significantly greater increase in UAW length in boys compared to girls during puberty may be important in explaining the male predisposition to collapse in adults [31]. In aggregate, the data suggest that pharyngeal airway length is an important factor in determining airway mechanics and risk of sleep apnea. UAW length may be important in explaining the male predisposition to pharyngeal collapse, the increased vulnerability to this disease in post-menopausal women (vs. pre-menopausal), and the development of the male OSA predisposition at puberty.

UAW muscle function and tissue characteristics

Since airway patency depends on both UAW anatomy and function, the activity of the dilator UAW muscle has drawn attention in OSA pathogenesis. Many

diseases such as muscular dystrophy and myopathy result in increased risk of OSA, probably secondary to the loss of protecting effect of the UAW dilators.

Three groups of muscles have been investigated in the context of the pathogenesis of OSA: (1) the muscles influencing hyoid bone position (geniohyoid, sternohyoid, etc.); (2) the muscle of the tongue (genioglossus); and (3) the muscles of the palate (tensor palatini, levator palatini). The activity of many of these muscles is increased during inspiration ("phasic muscles") thus stiffening and dilating the upper airway thereby counteracting the collapsing influence of negative airway pressure [32]. The genioglossus (GG) is the best-studied such muscle. The activity of the GG is substantially reduced (although not eliminated) during expiration when pressure inside the airway becomes positive and there is less tendency for collapse. Other muscles such as the tensor palatini do not generally demonstrate inspiratory phasic activity but instead maintain a relatively constant level of activity throughout the respiratory cycle [33], i.e. tonic or postural muscles. These two types of pharyngeal muscles are likely controlled by different groups of neurons within the brainstem that have different firing patterns relative to the respiratory cycle.

The activity of the pharyngeal dilator muscles can be influenced during wakefulness by a number of physiological stimuli. Chemical stimulation (rising $PaCO_2$ or falling PaO_2) can substantially augment the activity of these muscles [34]. Perhaps more importantly, negative pressure in the pharynx (which would tend to collapse the airway) markedly activates these muscles, which in turn counteracts this collapsing influence [35, 36, 37]. This response to negative pressure is likely driven by local pressure or stretch-sensitive receptors as it can be substantially attenuated by the application of topical anesthesia.

As OSA patients have an anatomically small airway, this negative pressure reflex is highly activated during wakefulness (greater airway negative pressure in the apnea patient), leading to augmented dilator muscle activity as a neuromuscular compensatory mechanism to protect airway patency. The genioglossus muscle in apnea patients functions much closer to its maximum capacity during wakefulness, compared to controls [38]. That negative pressure drives this augmented muscle activity is suggested by the observation that continuous positive airway pressure (CPAP) can reduce the level of activity in the genioglossus muscle of apnea patients to near normal levels [38] Thus, were it not for this increased activity of the pharyngeal dilator muscles, the airway of the apnea patient may substantially narrow or collapse during wakefulness. Therefore, the individual's propensity for upper airway collapse during sleep depends on two variables: (1) his/her predisposing anatomy; and (2) the level of pharyngeal dilator muscle activity.

The effect of sleep on UAW muscle activity probably plays an important role in the pathophysiology of OSA. The activity of tonic pharyngeal dilator muscles such as the tensor palatini is markedly reduced during NREM sleep (to 20–30% of awake values) while phasic muscles generally maintain waking levels of activity during stable NREM sleep [39]. This fall in tonic muscle activity conceivably contributes to the observed increments in airflow resistance commonly seen in normal individuals with the transition from wakefulness to sleep. Phasic muscle activity, on the other hand, remains stable or even slightly increased in normal subjects during stable NREM sleep in comparison with wakefulness [39, 40, 41]. However, the protective reflex activation of these muscles to negative pressure that can be observed during wakefulness is importantly diminished during sleep even in normal subjects. Using a model of passive negative pressure ventilation, a tight relationship between varying intrapharyngeal negative pressures and genioglossal muscle activation during wakefulness has been shown in both controls and in apnea patients. Using the same model, it has been observed that the relatively steep, linear relationship between negative epiglottic pressure and genioglossal EMG was markedly reduced during sleep [42]. At the transition from wakefulness to sleep there was also an important reduction in genioglossal activity in apnea patients. Thus, while the negative pressure reflex is able to maintain genioglossal EMG and airway patency during wakefulness, this reflex is unable to do so during sleep. Furthermore, it has been shown that the strong dependency of the dilator muscle activation on CO_2 that is seen during wakefulness is substantially diminished during either stage 2 or slow wave sleep [43]. Thus, the loss of the negative pressure reflex with the reduced responsiveness of dilator muscle activation to negative pressure and CO_2 leads to falling dilator muscle activity and airway collapse [37, 43, 44].

Several studies have assessed the age-related changes in UAW muscle characteristics and function. Oliven *et al.* [45] reported an age-related decrease in succinate dehydrogenase optical density (a marker of

oxidative capacity) in several UAW muscles but particularly in the genioglossus (the main tongue protrudor) of Wistar rats. In the GG muscle, they also found a significant decrease in type IIa and an increase in IIb fibers after the age of 18 months. The authors speculated that these changes in muscle characteristics may partially explain the increase in OSA seen in humans with aging. In humans, age was initially reported as a factor associated with increased pharyngeal resistance in men, but not in women [46]. Later research reported that the change in resistance from wakefulness to sleep was similar in young and older populations, but resistance itself was higher among older people [47]. More recent studies have shown an age-related increase in pharyngeal collapsibility and pharyngeal resistance during sleep, independent of body mass index (BMI) and gender [18]. Age was also reported to be associated with a decrement in respiratory effort during an obstruction [48], and in protecting genioglossus muscle activation [49]. Veldi *et al.* reported an age-related increase in soft palate elasticity, and a decrease in soft palate stiffness with age, although only in OSA patients [50]. We have recently reported that the pharyngeal dilator muscles of older subjects were less responsive to negative pressure stimuli than those of younger subjects (Figure 7.3) [1]. Thus, it seems that age-related changes in tissue characteristics and muscle function both contribute to the well-established age-related increase in respiratory disturbance index and OSA.

Ventilatory control instability (loop gain) and arousal effects

Some have argued that an intrinsic instability in ventilatory control mechanisms leads to variable output to the diaphragm and the pharyngeal muscles such that airway collapse occurs [51] when output to the upper airway muscles is at a minimum in an individual with a susceptible airway. The term loop gain is used to refer to the intrinsic stability or instability in the ventilatory control system. A system with high loop gain would be relatively unstable requiring only a minor perturbation to yielding periodic breathing. On the other hand, a system with low loop gain would be intrinsically stable with a regular breathing pattern persisting despite a major perturbation. Cyclical oscillations from the central pattern generator in the brainstem could therefore yield upper airway collapse when output to the pharyngeal dilator muscles was at its nadir in an individual who was anatomically predisposed. Younes *et al.* [52] studied 32 patients with OSA (12 severe) during sleep while their upper airway was stabilized with expiratory positive airway pressure. Susceptibility to periodic breathing was assessed by gradually increasing the gain of the ventilatory controller, using the proportional assist ventilation (PAV) technique to determine the point at which ventilation begins to oscillate. As implied above, an individual with high loop gain would require minimal assist to develop periodic breathing while an individual with low loop gain would have stable breathing despite high levels of PAV assist. Younes observed that of 12 patients with severe OSA, 9 developed periodic breathing, with recurrent central apneas, compared with only 6 of the 20 patients in the mild/moderate group. The authors concluded that the chemical control system is intrinsically less stable in patients with severe OSA than in patients with milder OSA, and speculated that this may contribute to the severity of OSA. In a later study, loop gain magnitudes were found to be similar in six OSA patients and five normal subjects, but the chemoreflex loop impulse response in the OSA subjects exhibited faster and more oscillatory dynamics, implying unstable upper airway mechanics and an underdamped chemoreflex control system [53]. This may be another important factor that promotes the occurrence of periodic obstructive apneas during sleep [53, 54].

Wellman *et al.* [55] have studied the interactions between airway anatomy and unstable ventilatory control. The authors quantified loop gain in a cohort of individuals using the PAV technique and assessed airway anatomy using the Pcrit (critical closing pressure). The rationale for this approach was based on the following logic. In an individual with a major anatomical abnormality (markedly positive Pcrit), ventilatory

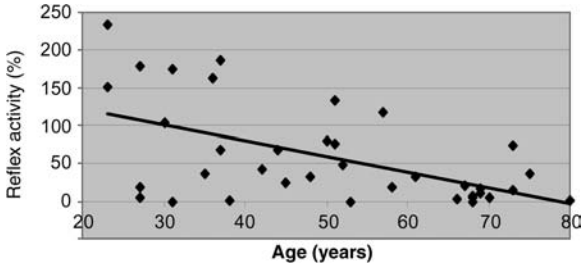

Figure 7.3. The decrease in negative pressure reflex with increasing age in normal subjects. With increasing age, there was a significant decrease in the genioglossal response to negative intrapharyngeal pressure pulses (R = 0.55; *P* = 0.001). (From Malhotra *et al.* [1].)

control would be relatively unimportant since the pharynx would tend to collapse purely on a biomechanical basis. On the other hand, in an individual with a very stable upper airway (markedly negative Pcrit), cyclical ventilatory output (high loop gain) would not be critical since the airway would be anatomically protected from collapse. For those with "intermediate anatomy" i.e. Pcrit near atmospheric pressure, loop gain may have a substantial impact on apnea severity. The authors showed a robust correlation ($r = 0.88$) between loop gain and AHI, suggesting that unstable ventilatory control may have an important impact within this subgroup. These data also have clinical relevance since one could speculate that measures to improve ventilatory stability (e.g. oxygen) would be most likely to have an effect among those in whom loop gain is playing a major pathophysiological role.

Despite the above observations, most studies have thus far failed to demonstrate a relationship between the higher susceptibility to OSA seen in men or with aging to this ventilatory control instability [56, 57, 58, 59]. Sin *et al*. reported an age-related decrement in hypercapnic ventilatory response, although the relevance of this finding to OSA is unknown [60]. Our group assessed loop gain in a cohort of younger and older healthy subjects without sleep apnea and observed loop gain values that were quite low in the elderly participants [59]. These data suggest that intrinsic instability in the ventilatory control system is not a critical factor in predisposing the elderly patient to sleep apnea. However, the PAV technique relies on a stable upper airway (using expiratory positive airway pressure) and stable state (no arousals) to reliably quantify loop gain. Thus, these factors (upper airway instability and state instability) may be neglected by the PAV technique. As a result, although the data do not suggest that loop gain is elevated in the elderly, this finding may reflect a methodological rather than a biological issue. Further work is clearly needed in this area.

Once the patient with apnea falls asleep and the cycle of repetitive airway obstruction begins, recurrent hypoxemia and hypercapnia develop. The rate at which these chemical disturbances evolve is related to a number of factors including: (1) the PaO_2 and $PaCO_2$ when the apnea begins; (2) the oxygen stores present in the individual, which relates to lung volume; and (3) whether there is continued effort during the apnea. The severity of hypoxemia and hypercapnia is also dependent on apnea length. Termination of the apnea generally requires a transient arousal from sleep thus activating the upper airway muscles and re-establishing airway patency. Without such an arousal, profound hypoxemia and hypercapnia would likely ensue. The possible mechanisms leading to arousal, include direct stimulation of peripheral and central chemoreceptors by rising $PaCO_2$ and falling PaO_2, afferent CNS input from the lung, chest wall, or upper airway receptors resulting from the increasing ventilatory effort that develops over the course of an apnea, or direct stimulation of the reticular activating system by respiratory neurons activated by the apnea process [61, 62]. Regardless of the explanation, arousal remains an important mechanism by which apneas are terminated, but at the same time arousals may increase the severity of the sleep disordered breathing by promoting greater ventilatory instability [63]. Whether any of these potential ventilatory control mechanisms or ventilatory responses to arousals is age dependent and may contribute to the age-related increase in OSA is unclear at this time.

Conclusions

Age-related changes in the anatomy and function of UAW may play a role in the increased prevalence of OSA with age. This chapter has not dealt, however, with the change in impact, associated symptoms, and consequences of OSA with increasing age. Bixler *et al.* [64] reported that the prevalence of sleep apnea tends to increase with age, but its clinical significance and severity decreases. Interestingly, although OSA probably results in increased morbidity and mortality during middle age, it has been suggested that OSA may have a protective role in patients aged ≥70 years [17], perhaps due to underlying factors leading to survival or as a result of developing protective mechanisms such as collateral coronary blood flow. Regardless of the mechanism, it appears that OSA prevalence does increase with age, although at a certain age it becomes less harmful. Thus, when clinically evaluating a patient for suspected OSA, age appears important in the assessment of both complaints and prognosis. Treatment decisions for sleep apnea need to be individualized, particularly in the elderly where the benefits may be modest.

Summary

Sleep apnea syndrome is a disorder characterized by repetitive episodes of cessation of breathing that occur during sleep. The most common form of apnea results

from repetitive partial or complete obstruction of the upper airway. Age-related changes in the prevalence of sleep apnea show that it is relatively common in children (peaking around age of 3 years), relatively uncommon in adolescents and young adults, and again common in middle-aged adults with increasing prevalence in the elderly. Several pathophysiological mechanisms have been proposed to explain the repetitive upper airway obstruction seen in obstructive sleep apnea. The current chapter focuses on age-related changes in such mechanisms in apneic and normal subjects, and on the potential relevance of these findings to obstructive sleep apnea. Generally, it seems that with increasing age the upper airway becomes longer (a prominent change in males in childhood, and females in adulthood) which makes the pharynx more vulnerable to collapse. In addition, upper airway dimensions may decrease with increasing age, parapharyngeal fat pad size increases, and pharyngeal resistance increases (in men). The respiratory effort during an obstruction may be reduced, and the protective upper airway muscle reflexes are attenuated with increasing age. However, reported changes in control of breathing and ventilatory instability have been inconsistent across various studies. All of these age-related changes, along with increases in body weight, may collectively explain the increase in prevalence of obstructive sleep apnea with increasing age.

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Part 2 Neuroendocrine and homeostatic changes in the elderly

Neuroendocrine correlates of sleep in the elderly

Theresa M. Buckley

Introduction

Key features of sleep in aging include a decrease in slow wave sleep (SWS), an increase in the frequency of awakenings and difficulty with sleep maintenance [1]. Time spent in lighter sleep (stages 1 and 2) increases and time spent in slow wave sleep (stages 3 and 4) decreases [1]. Percent time in REM sleep tends to remain constant, although it may decrease slightly. In addition to changes in sleep architecture, sleep onset and offset times shift to the earlier part of the evening. Advanced sleep phase syndrome is more prevalent with increasing age. Naps are more frequent as well. In aging with dementia, these changes are more pronounced.

In some cases, changes in neuroendocrine function with aging either contribute to or correlate with some of the changes in sleep with healthy aging [2]. In this chapter, we will discuss such changes in the context of the hypothalamic-pituitary-adrenal (HPA) axis, the somatotropin axis, the hypothalamic-gonadal (HPG) axes, and the orexin-hypocretin system. We also briefly discuss the thyroid axis as well as relationships with prolactin.

Changes in sleep associated with hormonal changes may be due to direct hormonal effects on sleep or secondary to other endocrine-induced physical symptoms that in turn affect sleep. In the following discussion, we will link changes in sleep with aging with changes in neuroendocrine systems with aging.

HPA axis

The hypothalamic-pituitary-adrenal (HPA) axis originates in the paraventricular nucleus of the hypothalamus where corticotropin-releasing hormone (CRH) is released (Figure 8.1). CRH is also released from extra hypothalamic sites in the brain such as the amygdala and the cerebral cortex. Hypothalamic CRH acts on the pituitary gland to release adrenocorticotropin releasing hormone (ACTH). Once released into the bloodstream, ACTH acts on the adrenal cortex to stimulate the production and release of cortisol.

Cortisol is released in a circadian-dependent fashion [3], with peak values occurring between 8 am and 9 am and the nadir occurring at about midnight. After the early morning peak, levels fall throughout the day. With sleep onset, there is a continuous drop towards the nadir. The trough surrounding the nadir is referred to as the quiescent period. After reaching the nadir, levels begin to rise progressively into the early waking hours [4, 5].

Connections from the SCN to the paraventricular nucleus of the hypothalamus help drive the baseline rhythmicity or circadian release of CRH. In addition, cortisol exhibits pulsatile secretion in the latter part of the night, which is thought to be linked to the ultradian pattern of rapid eye movement (REM) sleep cycles [6, 7]. REM occurs as cortisol falls and SWS starts as cortisol rises. In addition to its baseline circadian driven secretion, cortisol is also secreted in times of stress via the fight or flight response.

Both glucocorticoid (GR) and mineralocorticoid (MR) receptors mediate feedback of cortisol and their effects depend on location. Inhibitory GRs are located in the anterior pituitary and hypothalamus and inhibitory MRs are located in the hippocampus. Inhibitory feedback of cortisol to the anterior pituitary and

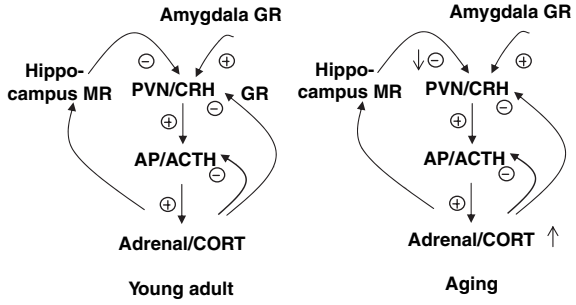

Figure 8.1. HPA axis and MR/GR feedback relationship in young and healthy aging adults. AP, anterior pituitary; CORT, cortisol. (Modified from Buckley & Schatzberg [2].)

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hypothalamus and hippocampus help restrain its further production and release. Inhibitory feedback from the hippocampus to the PVN, via the bed nucleus of the stria terminalis, also inhibits cortisol [8]. An MR agonist lowers nocturnal cortisol in healthy subjects [9]. By contrast, cortisol exerts positive feedback on CRH via GR stimulation at the level of the amygdala [10]. In addition, there is a positive reciprocal circuit between the amygdala and brainstem locus ceruleus [8, 11]. Via this circuit, amygdala CRH stimulates norepinephrine release from the locus ceruleus and vice versa.

Both MRs and GRs help modulate the cortisol rhythm. Mineralocorticoid activation is most evident at the time of the nocturnal nadir, or minimum, of cortisol [12]. By contrast, glucocorticoid receptor activity helps restrain cortisol at its maximum, or the acrophase.

HPA axis effects on sleep

Several studies suggest that nocturnal hypercortisolemia and elevated ACTH is associated with insomnia [13, 14, 15, 16], though not all studies agree. It is likely that the relationship between cortisol and sleep is largely mediated via CRH. Early studies showed that CRH increases sleep EEG frequency and awakenings [17]. More recent studies along similar lines of causality report HPA axis hyperactivity in insomnia without depression as evidenced by elevated evening and nocturnal cortisol and ACTH (Figure 8.2) [13, 14, 15, 16]. This effect is likely due to elevated CRH, perhaps by activation of the locus ceruleus norepinephrine pathway [18]. Norepinephrine is a commonly known wake-promoting neurotransmitter.

Though *exogenous* cortisol infusion may increase slow wave sleep, it likely does so via negative feedback inhibition on CRH in the paraventricular nucleus of the hypothalamus. The association between poor sleep and elevated *endogenous* cortisol and ACTH may be due to the fact that ACTH and cortisol are likely markers for elevated CRH.

In addition to the wake-promoting effect of CRH, wakefulness itself may result in elevated cortisol levels [7]. Debate exists as to whether elevated cortisol in insomnia is an epiphenomenon of the insomnia or a contributor to the insomnia. It may be both.

HPA axis changes with aging

Changes in the HPA axis and its rhythm with aging are described in Figure 8.3 (reviewed in [2, 19]). In healthy aging [20, 21, 22], the amplitude of the circadian rhythm of cortisol is decreased and its nocturnal average is elevated. Furthermore, its nadir and rhythm tend to be advanced. These changes may be secondary to primary changes in the activity of the circadian pacemaker, the suprachiasmatic nucleus.

Another likely contributor to changes in the cortisol rhythm with aging is change in MR activity in the

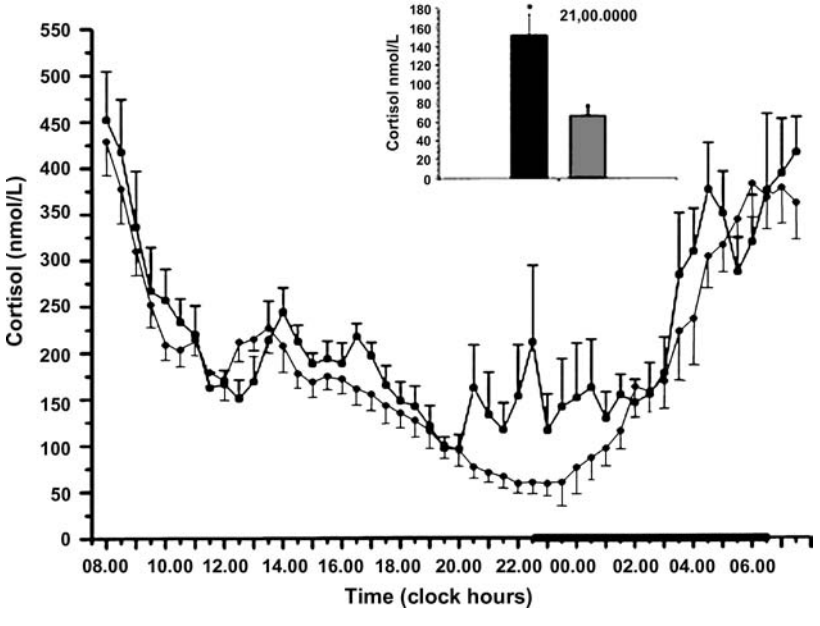

Figure 8.2. Nocturnal hypercortisolemia in insomnia. (From Vgontzas *et al.* [15].)

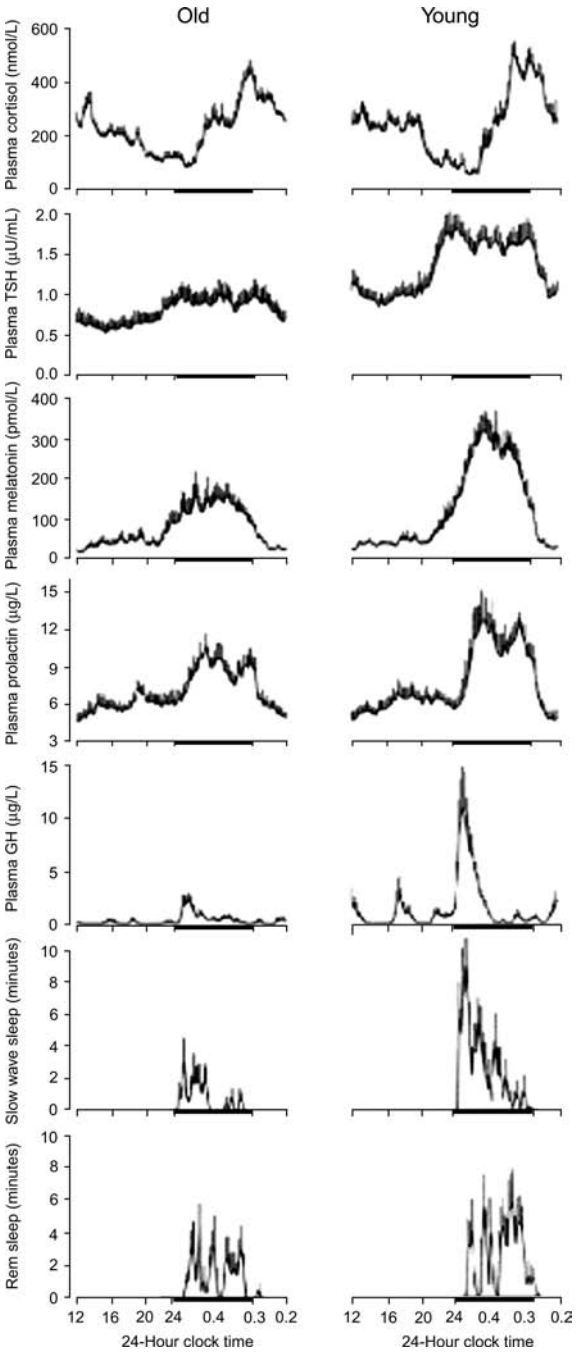

Figure 8.3. Neuroendocrine rhythms in young adults versus healthy aging. (From van Coevorden *et al*. [22].)

hippocampus [12, 23, 24, 25, 26, 27]. An important inhibitory circuit extends from the hippocampus to the paraventricular nucleus of the hypothalamus, which helps restrain HPA axis activity, particularly during the early nocturnal period. A decrease in the number or function of mineralocorticoid receptors in the hippocampus with healthy aging is expected to disinhibit the HPA axis and elevate the nocturnal nadir of cortisol. Regardless of the cause, the known nocturnal hypercortisolemia that occurs with aging may be a manifestation of increased CRH at night, which is also associated with aging.

Correlates of sleep and HPA axis changes with aging

Sleep changes in healthy aging include a reduction in the percentage of slow wave sleep [1]. Given that the amplitude of delta waves is decreased with age, it has been proposed that part of the reported decrease in SWS may be an artifact of sleep stage scoring rules, which include both amplitude and frequency criteria.

Some age-associated changes in HPA axis activity correlate with similarly associated changes in sleep. For example, if the cortisol circadian rhythm is a marker for increased CRH, elevated nocturnal CRH will contribute to higher frequency EEG (or decreased SWS), an increased number of awakenings and lighter sleep, all observed with aging. Similarly, the advance in the cortisol rhythm and nadir parallels the advance in sleep onset and offset. Finally, an inverse relationship between cortisol and melatonin has been reported in healthy aging, suggesting a potentially important interaction between the two hormones.

Somatotropin axis

Growth hormone-releasing hormone (GHRH) is produced and released from the arcuate nucleus of the hypothalamus. GHRH travels through the portal system to the anterior pituitary to cause the release of GH into the bloodstream. Grhelin, produced in the stomach, also stimulates GH secretion. Somatostatin inhibits GH release at the level of the hypothalamus.

Key actions of GH are to stimulate growth of muscle and bone. In liver, GH stimulates the release of insulin-like growth factor (IGF-1) which causes lypolysis of fat cells and protein synthesis in muscles, as well as skeletal growth.

Growth hormone is released in an intermittent pulsatile manner. Occasional bursts occur during the day (mostly in women) while its major burst of secretion occurs in the early nocturnal sleep period (in both women and men), about 1 hour after sleep onset. Between bursts of secretion, its level remains low and flat. Growth hormone-releasing hormone secretion

co-occurs with slow wave sleep in men. There is a reciprocal interaction between GHRH secretion and CRH secretion. As GHRH decreases, CRH increases and slow wave sleep decreases [28, 29].

There is an age-related change in GH secretion (Figure 8.4). Peak GH secretion occurs during adolescence and its secretion declines with age. While its secretion at night is important for normal development in adolescence, excess growth hormone can contribute to acromegaly and sleep apnea.

Not only does GHRH impact SWS, but SWS significantly impacts GH secretion [28, 29, 30, 31, 32].

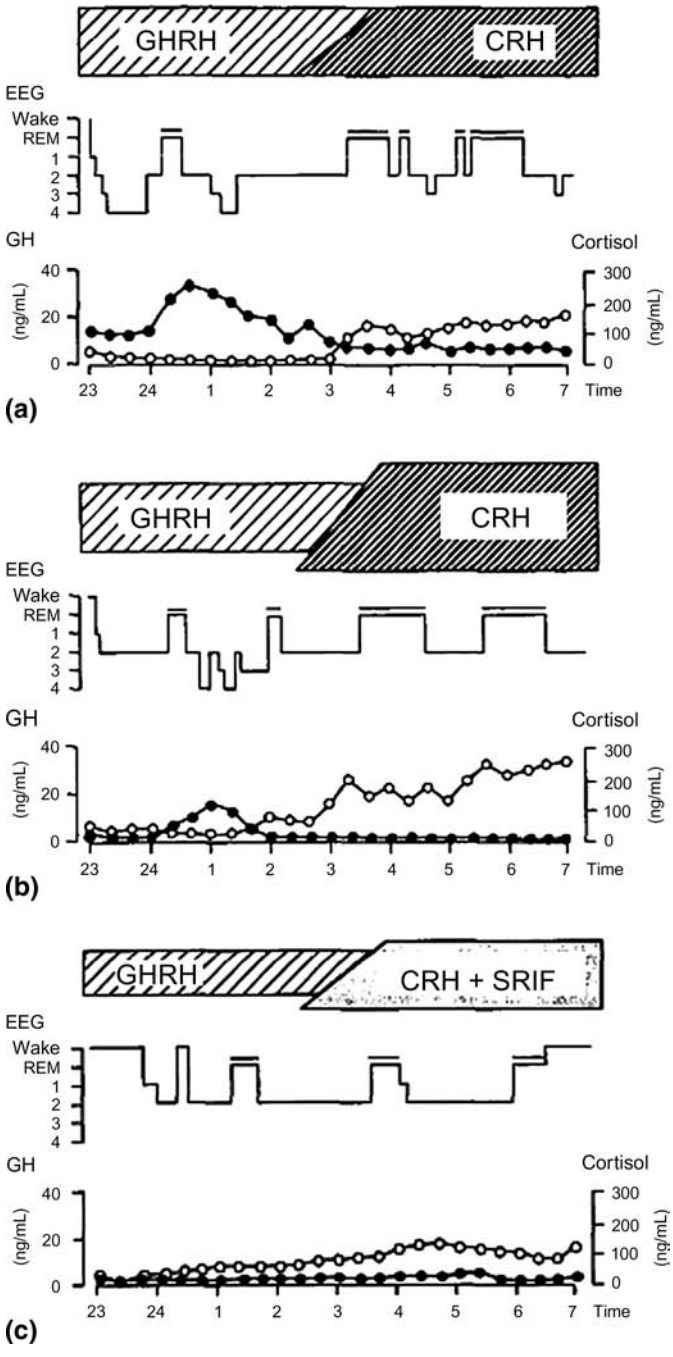

Figure 8.4. CRH and GHRH relationships in young subjects versus normal aging. (a) Young normal control; (b) patient with depression; (c) aged normal control. SRIF, somatotrophin release-inhibiting factor. (From Steiger & Holsboer [32].)

In fact, the onset of nocturnal sleep (regardless of its advance or delay) is temporally associated with a burst of GH secretion. Clinical examples attest to the importance of SWS in enhancing GH secretion. For example, gamma hydroxybutyrate (GHB) has been illicitly used by body builders to enhance SWS and to secondarily enhance GH secretion and body muscle mass. Conversely, the SWS-associated increase in GH is important for normal growth and development, particularly during adolescence. Disruption of SWS, such as from untreated obstructive sleep apnea, can interfere with normal growth.

The inverse relationship between GHRH and SWS as well as between CRH and GHRH provide the basis for influences of GHRH on sleep in aging [28, 29, 30, 31, 32]. The decline in magnitude of nocturnal GHRH with aging may contribute to the observed decrease in SWS in aging either directly or indirectly via the reciprocal relationship with CRH. Trials using GHRH analog therapies to help promote sleep in aging have produced varied results. Successful trials with intranasal administration of GHRH [33], which bypasses the blood–brain barrier, have been shown to promote slow wave sleep in aging. Conversely, somatostatin impairs sleep in the elderly [34].

Hypothalamic-gonadal axis (males)

Gonadotropin-releasing hormone (GnRH) is produced and released in the hypothalamus. It acts on the anterior pituitary to cause the release of both follicle stimulating hormone (FSH) and luteinizing hormone (LH) into the bloodstream. In males, GnRH acts on the Leydig cells of the testes to promote the production and release of testosterone. Testosterone secretion follows a circadian variation. Levels are highest at night then decline throughout the day and reach their lowest level in the evening [35].

Quality and quantity of sleep impact morning levels of testosterone [36]. Conversely, the effects of testosterone on sleep are not clear. However, some studies suggest an inverse relationship between overnight testosterone and sleep quality. In a study of 67 healthy men, aged 45 to 75 years [37], there was a positive correlation between sleep efficiency and mean overnight concentrations of testosterone. Similarly, wake after sleep onset (WASO) correlated negatively with overnight testosterone. This effect persisted, regardless of age.

There is a steady decline in testosterone with aging. There is also a loss in the diurnal rhythmicity and lower mean 24-hour levels [35]. Andropause is associated with decreased sexual drive, decreased cognitive function, decreased lean body mass, decreased bone mineral density, and increased visceral fat [38]. In addition, andropause is associated with elevations in interleukin-6 (IL-6) [38].

Prior studies suggesting a relationship between testosterone and sleep efficiency would imply that a decline in testosterone with andropause may contribute to some of the increased sleep fragmentation observed. Such an association would need further study. Testosterone replacement therapy has been used to offset the decline in testosterone with aging. Whether it improves sleep efficiency remains to be established. However, its use may also increase risk of sleep apnea [39]. Additionally, stress and sleep deprivation in young men are associated with decreased testosterone levels [40, 41]. Given an inverse relationship between cortisol and testosterone, it is plausible that insomnia in older men may additionally add to the natural decline in testosterone with age.

Hypothalamic-gonadal axis (females)

The hypothalamic-gonadal axis includes GnRH released from the hypothalamus. Its secretion begins in adolescence, at the time of puberty. GnRH is secreted in a pulsatile manner and acts on the pituitary to effect the release of both LH and FSH into the bloodstream. In females, FSH acts on the ovaries to promote the production and release of estrogen.

In females, the effects of gonadotropins on sleep are mediated via their effects on progesterone and estrogen. Progesterone is somnogenic and enhances slow wave sleep and REM sleep. Elevated progesterone early in pregnancy contributes to the sometimes marked hypersomnolence seen in the first trimester. Progesterone's somnogenic properties are thought to be secondary to agonist actions at the $GABA_A$ receptor complex [42], similar to the actions of a benzodiazepine on sleep.

The effects of estrogen on sleep are less clear. Prior to menopause, estrogen is produced in the form of estradiol by the ovary [43]. After menopause, the primary source of estrogen is via the formation of estrone in adipose tissue [43]. There is a link between the HPA axis and the hypothalamic-pituitary-ovarian (HPO) axis such that the HPA axis suppresses the HPO axis. Similarly, estrogen helps to restrain the HPA axis and noradrenergic pathways. A lack of restraint and subsequent HPA axis hyperactivity is theorized to contribute to insomnia in post-menopausal women [44].

A decline in sigma frequency EEG activity occurs after menopause in females. This abrupt change contrasts with the more gradual age-related decline in this frequency in males [45]. Although not all studies agree that estrogen replacement therapy can improve sleep, one study showed that an estrogen patch for 4 weeks improved REM sleep and decreased WASO during the first two sleep cycles [46]. Another study showed that progesterone replacement increased the amount of REM sleep and decreased WASO [42].

In addition to its neuroactive steroid properties on sleep itself, progesterone and estrogen influence the incidence of obstructive sleep apnea (OSA). In fact, some studies propose that primary sleep disorders are a chief cause of sleep complaints in post-menopausal women rather than the direct neuroactive effects of progesterone and estrogen themselves [47, 48]. Although restless legs syndrome and periodic leg movement disorder also increase with age, an increase with menopause does not occur. Of the primary sleep disorders, there is an increased incidence of OSA with menopause that may be related to the effects of estrogen and progesterone decline.

The effects on OSA are multifactorial. Progesterone is a respiratory stimulant and decreases both central and obstructive sleep apnea events in men [49]. Medroxyprogesterone has been proposed to improve chronic obstructive pulmonary disease in post-menopausal women [50]. In one study of the effects of menstrual cycle on upper airway resistance, upper airway resistance was lowest in the luteal phase when compared to the follicular phase [51]. The decrease during the luteal phase is attributed to benefits of increased progesterone [51]. Additionally, progesterone has been reported to affect genioglossus muscle tone. Thus, it has been theorized that a relaxation in upper airway muscle tone with a decline in progesterone may also contribute to the increase in sleep disordered breathing in menopause [52].

One study of 53 women demonstrated that those with an apnea-hypopnea index greater than 10 had significantly lower levels of progesterone and estradiol than those with an index less than 10 [53]. Consistent with this finding, one pilot study suggested that HRT (with a combination of estrogen and progesterone) may decrease severity of sleep apnea in post-menopausal women [54].

Although the role of hot flashes in menopause-related sleep complaints has been debated, it does fit the model as a precipitating factor in setting the stage for new onset psychophysiological insomnia. For example, hot flashes can cause awakenings and promote the development of psychophysiological insomnia that may persist, even after the hot flashes cease [55]. Thus, treatment using behavioral interventions, just as in other etiologies of psychophysiological insomnia, may be helpful. Finally, a decline in estrogen may play a role for increased incidence of mood disorders in menopause with its associated insomnia. For example, the HPG axis helps restrain HPA axis activity. Furthermore, estrogen plays a role in serotonin and norepinephrine regulation [56].

Despite the known effects of estrogen and progesterone on sleep as discussed above, a recent cohort study of 589 women (pre-menopausal, peri-menopausal, and post-menopausal) casts doubt on the existence of menopause-related sleep problems. They report that menopause is not associated with objective changes in sleep by polysomnography, despite less subjective sleep satisfaction in post-menopausal women [57]. Given the large size of this study and its conclusions, further study is required to better elucidate the actual presence and mechanism for increased menopause-related sleep complaints. An important point is that menopause-related sleep complaints should not always be attributed to hormonal changes, but to a search for and treatment of underlying sleep disorders.

Hypocretin-orexin system

The hypocretin-orexin system is important for influencing many aspects of sleep-related brainstem nuclei activity. The hypocretin neurons, located in the lateral hypothalamus, have important stimulatory projections to the locus ceruleus (norepinephrine), tuberomammary nucleus (histamine), and dorsal raphe nucleus (serotonin), whereby they help induce wakefulness. In turn, these monoaminergic brainstem-alerting neurons inhibit the sleep-active ventrolateral pre-optic nucleus (VLPO) GABA system. Through these projections, the hypocretin-orexin system acts as a modulator of the sleep–wake state, helping to stabilize the sleep–wake switch [58].

In addition to this modulating effect on brainstem nuclei involved in sleep regulation, there is a circadian rhythm to the hypocretin system. Hypocretin is important for maintaining wakefulness and sleep consolidation [59], with highest levels in the late evening before sleep onset. In normal sleep, the tendency to be asleep or awake is driven by a two-component model [60]

that combines the influences of a circadian alerting signal (tendency to wakefulness) with a homeostatic sleep drive (tendency to sleep). It is thought that a lack of hypocretin, such as occurs in narcolepsy, leads to a reduced circadian alerting drive. The pattern of sleep and wakefulness is thus greatly influenced by the homeostatic system. In such a model, the tendency to be awake or asleep depends on past wakefulness. Thus, we see more frequent naps and difficulty with maintaining sleep at night in narcolepsy.

In aging, recent research delineates important changes in the hypocretin-orexin system that may influence some of the sleep changes observed. For example, less cerebrospinal fluid (CSF) hypocretin-1 (10% decline) is found in the CSF of old rats, compared to young and middle-aged rats [61]. Other researchers have reported a decrease in hypocretin receptor mRNA in mouse brain contributing to changes in sleep in aging [62], as well as diminished projections from the hypocretin system to brainstem nuclei [63].

Taken together with what we know about narcolepsy, a reduction in hypocretin-orexin function in aging contributes to a sleep–wake pattern in aging in the direction of that seen with narcolepsy: difficulty maintaining wakefulness during the day with more frequent naps and difficulty maintaining sleep at night. Another study reported a decrease in pre-pro orexin gene and orexin A and B levels in the lateral hypothalamus with aging [64]. It was hypothesized that a destruction of the orexin system may contribute to decreased vigilance as well as endocrine and autonomic changes seen in aging [64]. A similar age-related decline in hypocretin (orexin) receptor 2 messenger RNA levels is found in mouse brain [62]. Further study of the role of the hypocretin-orexin system in aging may also give clues to the phenomena of advanced sleep onset and offset as well as potential modulating influences on other hormones important to sleep–wake modulation (such as CRH, GHRH).

Prolactin

In contrast to the effects of GHRH and CRH on sleep, there are no clear effects of prolactin in this regard. However, there is a clear effect of sleep on prolactin. In fact, sleep onset is associated with a rise in prolactin levels [22]. This effect occurs regardless of the time of sleep onset, whether nocturnal or during a daytime nap. The rise in prolactin is thought to be associated with a simultaneous decrease in dopamine, as dopamine helps restrain prolactin release.

With healthy aging, there is a tendency for the amplitude of prolactin release to decrease during sleep in many, but not all subjects [22]. The cause of this blunting is not clear. For example, disruption of sleep that occurs in healthy aging can theoretically interfere with prolactin release. Although prolactin does not have a clear impact on sleep, a positive correlation between the amount of REM sleep and the magnitude of prolactin release at the acrophase has been reported [65]. This is reported in aged but not young subjects. Prolactin levels appear further involved in immune function[65]. Thus, further study on prolactin and sleep with aging may yield greater insight into disease prevention with aging.

The thyroid axis

The thyroid axis includes thyrotropin-releasing hormone (TRH) synthesized in the hypothalamus. TRH is released in a pulsatile manner via the median eminence and acts on the pituitary to cause the release of thyroid-stimulating hormone (TSH). In turn, TSH acts on the thyroid gland to stimulate the production and release of T3 and T4. T3 and T4 provide inhibitory feedback to TSH release at the level of the pituitary. Actions of T3 and T4 include metabolism of carbohydrates and fats, as well as calorigenesis. Thyroid hormones can also augment the actions of other hormones such as glucocorticoids and growth hormone.

TSH is secreted in a circadian-dependent pattern with peak levels occurring during sleep. The nadir occurs in the afternoon [22]. In addition to the circadian-dependent rise at night, sleep actually inhibits TSH secretion. In sleep deprivation, the circadian-dependent increase in TSH at night is further enhanced [66]. In aging, the pulsatile and circadian release of TSH is preserved [22] as are the nadir and acrophase. The key difference is that the amplitude of TSH at the acrophase is decreased in aged men as is the overall 24-hour secretion [67]. Theoretically, if sleep helps inhibit nocturnal TSH, one would expect an increase in maximum secretion at the acrophase in aging, as opposed to a decrease. TRH stimulation tests of TSH in young and healthy men suggest that the decrease in TSH with aging is likely secondary to decreased responsiveness of the pituitary to TRH with age [67].

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Part 2
Chapter
9

Neuroendocrine and homeostatic changes in the elderly

Melatonin, aging, and Alzheimer's disease

Daniel P. Cardinali and Michal Karasek*

Introduction

When it was originally discovered melatonin was thought to be primarily a skin-lightening molecule that acted on amphibian melanocytes [1]. Subsequently, melatonin was found to be present in all vertebrates, rhythmically secreted by the pineal gland, and involved in regulation of circadian and seasonal rhythms [2, 3]. In its role as a regulator of the body's most basic rhythms, melatonin secretion peaks at night, thus transmitting information about darkness, and then is suppressed by light, normally during the daytime hours, although secretion is readily reduced by the occurrence of light, whenever this may happen.

Melatonin is known to be synthesized in many vertebrate tissues and is almost ubiquitously present in organisms ranging from bacteria and protozoa to plants, fungi, and invertebrates [4]. The spectrum of melatonin's known effects now exceeds by far the dermatological actions that the original discoveries presumed. Although in humans circulating melatonin is synthesized mostly in the pineal gland, it can also be produced in several other organs (e.g. retina, extra-orbital lachrymal gland, Harderian gland, gastrointestinal tract, blood platelets, bone marrow cells, etc.) [3, 5].

Biosynthesis and catabolism of melatonin

The mechanism of synthesis of melatonin, as defined in the 1960s, largely by Axelrod [6], is depicted in Figure 9.1. The first step in melatonin formation is the uptake of the amino acid L-tryptophan from the circulation into the gland. Within the pinealocyte tryptrophan-5-hydroxylase (L-tryptophan, tetrahydropteridine: oxygen oxidoreductase, EC 1.14.16.4) catalyzes the conversion of L-tryptophan to 5-hydroxytryptophan, which is then decarboxylated by L-aromatic amino acid decarboxylase (EC 4.1.1.28) to serotonin. The next step, i.e. *N*-acetylation of serotonin to *N*-acetylserotonin, is catalyzed by arylalkylamine *N*-acetyltransferase (AA-NAT, acetyl CoA:aryl-amine *N*-acetyltransferase, EC 2.3.1.5).The final step in the pathway is the *O*-methylation of *N*-acetylserotonin to melatonin by hydroxyindole-*O*-methyltransferase (*S*-adenosyl-L-methionine:*N*-acetyl-serotonin-*O*-methyltranferase, EC 2.1.1.4) (1, 2, 4). Alternately, but at lower flux rates, melatonin can be formed via *O*-methylation of serotonin and subsequent *N*-acetylation of 5-methoxytryptamine, or by *O*-methylation of tryptophan followed by decarboxylation and *N*-acetylation.

Once synthesized, melatonin is not stored in pineal cells but is quickly released into the bloodstream where it circulates, 70% of which is bound to albumin [7]. Besides the blood, melatonin is also present in other body fluids, including saliva, cerebrospinal fluid (CSF), bile, semen, and amniotic fluid. Mean endogenous melatonin production rates have been calculated to be about 30 μg/day [8]. The half-life of melatonin in serum is 30–60 minutes [9].

Circulating melatonin is metabolized primarily in the liver, and secondarily in the kidney. It undergoes 6-hydroxylation to 6-hydroxymelatonin, catabolized by hepatic P_{450} mono-oxygenases, followed by sulfate or glucuronide conjugation to 6-hydroxymelatonin sulfate (90%) or 6-hydroxymelatonin glucuronide (10%) (Figure 9.1). About 5% of serum melatonin content is excreted unmetabolized in urine. For many years, melatonin was thought to be almost exclusively metabolized by 6-hydroxylation. This may be largely true for the circulating hormone, but not necessarily for tissue melatonin. Especially in the central nervous system, oxidative pyrrole-ring cleavage prevails and no 6-hydroxymelatonin was detected after melatonin

*Professor Michal Karasek passed away on 18 February 2009. He was an outstanding scientist with a real passion for pineal research. We will miss his warm personality and charm.

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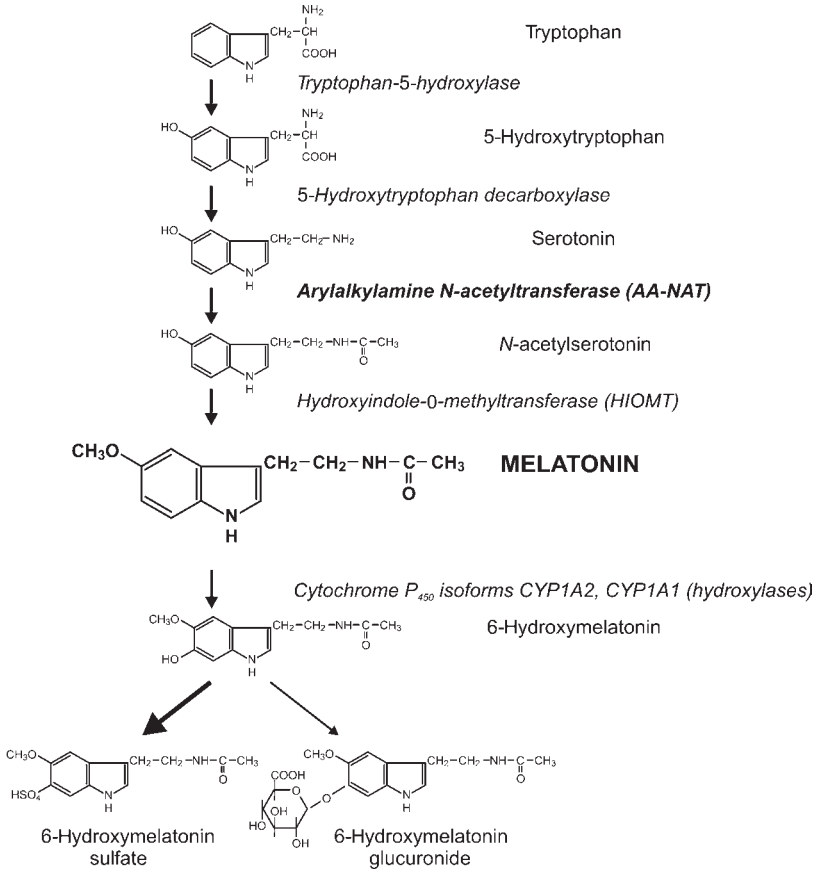

Figure 9.1. Biosynthesis of melatonin.

injection into the cisterna magna [10]. This may be particularly important because much more melatonin is released via the pineal recess into the CSF than into the circulation [11]. The primary cleavage product is N^1-acetyl-N^2-formyl-5-methoxykynuramine (AFMK), which is deformylated, either by arylamine formamidase or hemoperoxidases to N^1-acetyl-5-methoxykynuramine (AMK). Numerous enzymatic (indoleamine 2,3-dioxygenase, myeloperoxidase), pseudoenzymatic (oxoferryl hemoglobin, hemin), photocatalytic or free-radical reactions of melatonin lead to the same product, AFMK [4]. Pyrrole ring cleavage may contribute to about one third of the total melatonin catabolism. Other oxidative catabolites are cyclic 3-hydroxymelatonin, which can also be metabolized to AFMK, and a 2-hydroxylated analog, which does not cyclize, but turns into an indolinone [4]. Additional hydroxylated or nitrosated metabolites have been detected, which appear to represent minor quantities only. AFMK and AMK also form metabolites by interactions with reactive oxygen and nitrogen species [12].

Melatonin´s circadian rhythm and its regulation

Melatonin has a well-defined circadian rhythm with the peak in its production in the pineal gland occurring during the daily dark period (80–90% of melatonin is synthesized at night) (Figure 9.2). The rhythm of melatonin synthesis/secretion is generated by the circadian pacemaker (oscillator, biological clock) situated in the suprachiasmatic nucleus (SCN) of the hypothalamus, and is synchronized to 24 hours primarily by the light–dark cycle acting via the SCN. During the day serum concentrations of the hormone are low (typically <10–20 pg/mL), significantly increase at late evening, and reach peak values between 24:00 and 03:00 hour (80–120 pg/mL). There is a very close relationship between the rhythm of melatonin production and its major urinary metabolite – 6-sulfatoxymelatonin, a fact that is convenient for studying melatonin rhythms experimentally.

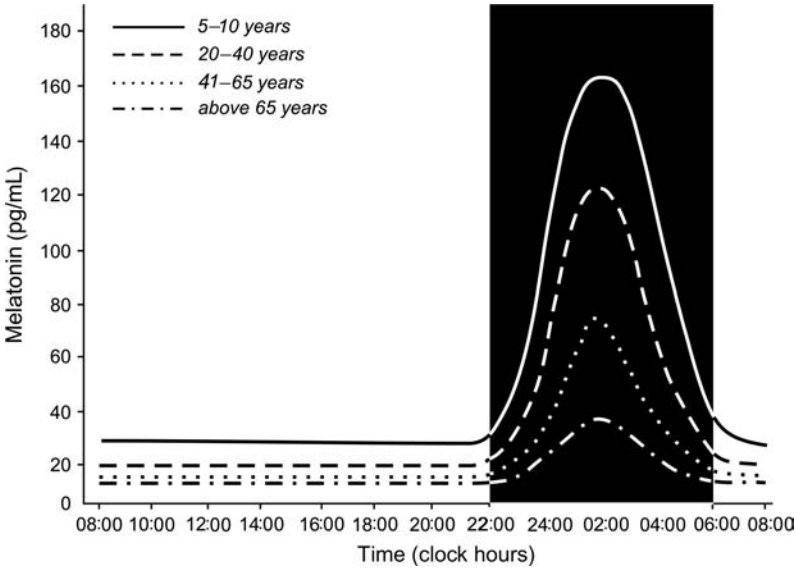

Figure 9.2. Circadian profiles of serum melatonin concentrations in humans at various age; black area = period of darkness.

The synthesis of melatonin is mainly controlled by environmental lighting. Photosensory information arrives at the pineal via the polyneuronal pathway that begins in the retina and involves the retinohypothalamic tract, SCN, subparaventricular hypothalamic areas, medial forebrain bundle, reticular formation, intermediolateral cell column of the spinal cord, superior cervical ganglia, internal carotid nerve, and nervii conarii [13]. Post-ganglionic sympathetic nerve fibers that terminate in the pineal promote the release of norepinephrine (NE), an action that is crucial for controlling melatonin synthesis. NE binds to pinealocyte β-adrenergic receptors (and partially α-adrenergic receptors), activating adenylate cyclase through GTP-binding protein in the cell membrane, and increasing cAMP levels. Stimulation of α-adrenergic receptors potentiates the β-stimulation, with participation of calcium ions, phosphatidylinositol, diacylglycerol, and protein kinase C [14]. The regulation in the cAMP/PKA pathway includes gene expression through pCREB binding and a negative feedback loop involving ICER (inducible cAMP early repressor). Additionally, cAMP mediates AA-NAT phosphorylation, which enhances enzymatic activity and promotes a stabilizing complex with 14–3–3 proteins. Noradrenergic stimulation also upregulates MAP kinase phosphatase 1, which prevents suppression by the MAP kinase pathway [14]. Another Ca^{2+}-dependent feedback loop involves the binding of DREAM (downstream regulatory element antagonist modulator) to the downstream regulatory element (DRE).

The rhythm in melatonin concentrations appears in humans soon after birth, during the 6th–8th week of life, and is well established by 21–24 weeks of life [15]. The amplitude of the nocturnal peak in melatonin secretion is greatest between 4 and 7 years of age. There is a drop in melatonin concentrations around maturation; the values remain relatively stable in human subjects up to the age of 35–40 years, and thereafter diminish gradually, until by the age of 70 the nocturnal concentrations are similar to those seen during the day [16]. As a consequence, in advanced age many individuals do not exhibit a day–night difference in melatonin secretion (Figure 9.2). The amplitude of nocturnal melatonin secretion is believed to be genetically determined and shows considerable variation among individuals. Thus, some individuals produce significantly less melatonin during their lifetime than others. However, the circadian profile of melatonin has been found to be highly reproducible over a 6-week period in the same subject [17]. Melatonin synthesis is rapidly suppressed in the dark phase by acute exposure to light of sufficient intensity, although there are substantial individual variations in human sensitivity to light among individuals that may be both genetically and environmentally determined.

Biological activity of melatonin

Melatonin is highly pleiotropic. Classical effects on the control of circadian and seasonal rhythms are attributed to G_i protein-coupled membrane receptors, MT_1 and MT_2, differing in ligand affinity [18].

Both are involved in circadian melatonin feedback at the SCN. MT_2 receptors are involved in the phase-shifting effect of melatonin. MT_1 receptors, having a higher affinity, cause acute suppressions of neuronal firing and are involved in the increase of circadian rhythm amplitude produced by melatonin [18]. Other effects are related to nuclear receptors of lower ligand sensitivity, RZR/RORα and RZRβ [15], but in these cases functional significance and target genes are less clear.

Melatonin also exhibits immunomodulatory properties, which are mediated via membrane and nuclear receptors [19]. Evidence of melatonin's activating effects has been demonstrated in T cells, B cells, natural killer (NK) cells, and monocytes, and includes thymocyte proliferation, release of cytokines, met-enkephalin and other immuno-opioids, and anti-apoptotic effects, including glucocorticoid antagonism. Signaling mechanisms for these effects are only partially understood. For example, in thymocytes and lymphocytes, cAMP is decreased via MT_1 or MT_2 receptors. However, melatonin also potentiates VIP-induced increases in cAMP in lymphocytes. Anti-inflammatory actions of melatonin are related to the inhibition of PGE_2 effects and, in particular, COX-2 downregulation, which may be transmitted by its metabolite AMK [20].

Melatonin's immunomodulatory actions appear to be the basis for the antitumor effects that have been attributed to it. Other oncostatic actions involve MT_1/MT_2-dependent suppression of linoleic acid uptake or estrogen receptor downregulation [21].

A developing and very important area of melatonin research is antioxidative protection, a crucial aspect in neuroprotection [4]. Antioxidant actions of melatonin are observed at different levels, including attenuation of free-radical activity by antiexcitatory and anti-inflammatory effects. This is not restricted to scavenging, although melatonin efficiently interacts with various reactive oxygen and nitrogen species as well as organic radicals, but includes upregulation of antioxidant enzymes (glutathione peroxidase, glutathione reductase, γ-glutamylcysteine synthase, glucose 6-phosphate dehydrogenase, sometimes Cu,Zn- and Mn-superoxide dismutases and catalase) and down-regulation of pro-oxidant enzymes (NO synthases, lipoxygenases). Mechanisms of the enzyme inductions have not been identified, whereas suppression of Ca^{2+}-dependent NOS may involve melatonin binding to calmodulin, an effect also playing a role in cytoskeletal rearrangements [4]. Additional antioxidant effects may be mediated by binding to quinone reductase 2, which had previously been assumed to represent another melatonin receptor (MT_3). Antioxidative protection is particularly evident in senescence-accelerated mice. The effects of melatonin on mitochondria have also been the focus of interest. Melatonin appears to play a key role in safeguarding the respiratory electron flux and reducing oxidant formation by lowering electron leakage, effects shared by AMK, and inhibiting the opening of the mitochondrial permeability transition pore (mtPTP) [22].

Melatonin and aging

The worldwide prolongation of the mean life expectancy as well as the drastic reduction of fertility rate have resulted in a rapid increase in the size of the elderly population (over the age 65), both in numbers and as a proportion of the whole. As a consequence, the increasing number of people who are reaching an advanced age raises many social and economic problems as beneficiaries of health and pension funds are supported by a relatively smaller number of potential contributors (i.e. those in the economically active age of 18–65). In addition, the number of people suffering from age-related diseases (such as atherosclerosis, neoplastic disease, neurodegenerative diseases) has increased. Therefore, there is an active search for therapeutic agents that may improve the quality of life of the elderly. It has been suggested that melatonin may be a compound that could potentially fulfil this role [5, 23].

Pineal secretory activity undergoes significant changes with age. Indeed, a progressive lowering of nocturnal melatonin peak becomes apparent when going from adulthood to senescence. The possible mechanisms by which melatonin secretion declines with age may depend on some regressive changes such as the calcification of the pineal gland, although these changes alter neither the pineal's histology nor its enzymatic activity [24, 25].

The amplitude of nocturnal melatonin secretion, which is probably genetically determined, closely influences the melatonin signal [26]. The decrease of melatonin amplitude and/or of the duration of its nocturnal peak could be responsible for an internal temporal desynchronization, with the consequence of reducing the individual's adaptability to the internal and external environmental changes and thus to the deterioration of health.

Therefore, it is interesting that in one study of centenarian subjects, a highly selected group that could be considered a good expression of successful aging, the nocturnal excretion of 6-sulfatoxymelatonin was found to be significantly greater than diurnal levels; when expressed as a percent of the total 24-hour amount the diurnal and nocturnal excretion rate of the centenarians was found to be similar to those of young subjects. Further, no differences between the two urine samples were found, thus suggesting that the circadian organization of melatonin had been maintained in the older subjects to a greater extent than in the younger ones [27].

Since melatonin is a short-lived molecule, its physiological actions have also been found to be limited in duration particularly with regard to its effects on sleep [28, 29, 30]. Hence it was felt that a melatonin molecule with a longer half-life will have a better opportunity to activate melatonin receptors for influencing sleep properties and for promoting sleep efficiency [31]. In addition, to address the problem of melatonin´s short bioavailability, a slow-release formulation of melatonin (Circadin™, Neurim, Israel) has been developed and has recently been approved by the European Medicines Agency for treating insomnia in the elderly.

Melatonin has been used successfully in the treatment of insomnia [30] and circadian rhythm sleep disorders [32, 33]. For example, the slow-release formula of melatonin Circadin improves sleep quality, morning alertness, sleep onset latency, and quality of life in middle-aged and elderly insomnia patients [34, 35, 36]. Since sleep disturbances constitute the main symptom of depressive disorders, and additionally because disturbances of melatonin secretion have been documented in patients with major depressive disorders [37], melatonin has also been tried in the treatment of depression [38].

In view of the need for longer-acting melatonergic agonists that improve sleep efficiency without causing drug abuse or dependency, ramelteon (Rozerem™, Takeda) was developed. Ramelteon, which acts via MT_1/ MT_2 melatonergic agonism, has been found to be clinically effective for improving total sleep time and sleep efficiency in insomniacs [39]. Agomelatine (Valdoxan™, Servier), is another MT_1/MT_2 melatonergic agonist that also displays antagonist activity at 5-HT_{2C} serotonin receptors. Agomelatine has been found to be effective in treating depression and sleep disurbances in patients with major depressive disorders [40, 41].

Melatonin and Alzheimer´s disease (AD)

Alzheimer's disease, a neurodegenerative process of still uncertain etiology, is the most common type of dementia among the elderly, with an estimated prevalence of 18–25 million patients worldwide. It is characterized by the development of senile plaques and neurofibrillary tangles, which are strongly associated with neuronal malfunction and eventually loss [42]. During the past decades, two major pharmacological strategies have been designed for the treatment of AD that include cholinergic and non-cholinergic interactions. The former [43] is based on the idea that the loss of cholinergic neurotransmission, associated with the development of the disease, is responsible for memory, behavior, and learning disorders. Interestingly, a number of oxidation products of melatonin derivatives have recently been shown to exhibit acetylcholinesterase inhibitory activity [44].

Several studies show that melatonin levels are lower in AD patients compared to age-matched control subjects [45, 46, 47, 48, 49, 50, 51]. CSF melatonin levels decrease even in pre-clinical stages when the patients do not manifest any cognitive impairment (at Braak stages I–II) [52, 53], suggesting that the reduction in CSF melatonin can be an early trigger and marker for AD [54, 55]. It is not known whether the relative melatonin deficiency is either a consequence or a cause of AD, although it seems clear that the loss in melatonin aggravates the disease.

There is evidence that melatonin, as a chronobiotic agent, is effective as a treatment for irregular sleep–wake cycles and sundowning symptoms in AD patients [56, 57, 58, 59, 60, 61, 62, 63, 64, 65]. Initially, open studies in small groups of dementia patients having sleep disturbances indicated that melatonin (3 mg p.o. for 21 days) decreased sundowning and reduced variability of sleep onset time [56]. In another study of 10 individuals with MCI symptoms, the administration of 6 mg of melatonin improved sleep, mood, and memory [57]. Seven AD patients who exhibited irregular sleep–wake cycles, and who were treated with 6 mg of melatonin for 4 weeks, showed a significantly reduced percentage of night-time activity as compared to a placebo group [58]. The efficacy of 3 mg melatonin/day at bedtime in improving the sleep and alleviating sundowning was also shown in 11 elderly AD patients [59] and in 7 AD patients of another study [60]. Long-term administration of melatonin in doses

of 6–9 mg to 14 AD patients with sleep disorders and sundowning agitation for a period of 2–3 years improved sleep quality and suppressed sundowning [61]. Another open study on 45 AD patients with sleep disturbances, in which 6 mg of melatonin was given daily for 4 months, confirmed sleep improvement and suppression of sundowning [62]. In a randomized, controlled trial that was performed in two nursing homes, the efficacy of adding melatonin to light therapy for treating rest–activity (circadian) disruption in institutionalized patients with AD was evaluated [66]. The experimental subjects received 1 hour of morning light exposure (>2 500 lux) and 5 mg melatonin or placebo in the evening. After 10 weeks of treatment the melatonin-treated group showed significant improvement in daytime somnolence as indicated by a reduction in the duration of daytime sleep, an increase in daytime activity, and an improvement in day:night sleep ratio as assessed by actigraphy [66].

Along with changes in the sleep–wake cycle, cognitive alterations were also observed in some non-AD patients who had received melatonin, thus prompting a halting of the experimental treatment in these individuals [61]. These findings in open studies were confirmed in double-blind, placebo-controlled observations, with regard to sleep–wake rhythmicity and cognitive and non-cognitive functions [63]. In a larger multicenter, randomized, placebo-controlled clinical trial, two dose formulations of oral melatonin were applied: 157 subjects with AD and night-time sleep disturbance were randomly assigned to one of three treatment groups: (1) placebo, (2) 2.5 mg slow-release melatonin, or (3) 10 mg melatonin given daily for 2 months [64]. In this study melatonin facilitated sleep in a certain number of individuals, but collectively the increase in nocturnal total sleep time and decreased wake after sleep onset, as determined on an actigraphic basis, were only apparent as trends in the melatonin-treated groups. On subjective measures, however, care-giver ratings of sleep quality showed significant improvement in the 2.5-mg sustained-release melatonin group relative to placebo [64].

Large interindividual differences among patients suffering from a neurodegenerative disease are not uncommon and may account for the erratic results seen in many of the reported studies. Indeed, the circadian oscillator system is seriously affected in AD patients showing severe sleep disturbances and the efficacy of melatonin should be expected to also depend on disease progression.

If the expectation of melatonin activity in AD is to be neuroprotective, the treatment must be initiated at the earliest possible stage of the disease. Mild cognitive impairment (MCI) is an etiologically heterogeneous syndrome characterized by cognitive impairment shown by objective measures adjusted for age and education in advance of dementia. Approximately 12% of MCI patients convert to AD or other dementia disorders every year. Since MCI may represent prodromal AD it should be adequately diagnosed and treated [67]. The degenerative process in AD brain starts 20–30 years before the clinical onset of the disease. During this phase, plaque and tangle loads increase and at a certain threshold the first symptom appears [52, 53].

In a recent study, a retrospective analysis of initial and final neuropsychological assessment of 50 MCI outpatients, 25 of whom had received daily 3–9 mg of a fast-release melatonin preparation p.o. at bedtime for 9–18 months, was published [68]. Melatonin was given in addition to the standard medication prescribed by the attending psychiatrist. Patients treated with melatonin showed significantly better performance in Mini–Mental State Examination and the cognitive subscale of the AD Assessment Scale. Neuropsychologically a better performance was found in melatonin-treated patients. Abnormally high Beck Depression Inventory scores decreased in melatonin-treated patients, concomitantly with an improvement in wakefulness and sleep quality [68]. Hence, melatonin can be a useful add-on drug for treatment of MCI in a clinic environment.

The mechanisms that account for the therapeutic effects of melatonin in AD and MCI patients remain to be defined. Since the symptomatic actions have a certain delay to become apparent, they may be related to melatonin´s chronobiological effect. However, there is information indicating that the neuroprotective activities of melatonin against the amyloid-β peptide are not mediated by melatonin membrane receptors [69].

As mentioned above, melatonin has multiple actions as a regulator of antioxidant and pro-oxidant enzymes, radical scavenger, and antagonist of mitochondrial radical formation. The ability of melatonin and its kynuramine metabolites to interact directly with the electron transport chain by increasing the electron flow and reducing electron leakage are unique features by which melatonin is able to increase the survival of neurons under enhanced oxidative stress [12, 70, 71, 72].

Pappolla and his co-workers were the first to describe a potent neuroprotection against the toxicity of amyloid-β peptide in AD [73]. In fact, application of melatonin prevented the death of neuroblastoma cells exposed to amyloid-β peptide. Since then, the antifibrillogenic actions have been demonstrated in vitro, also in the presence of profibrillogenic apoE4 or apoE3, and in vivo in transgenic mouse models of AD (for references see [74, 75, 76]). It seems feasible that the efficacy of melatonin to improve the clinical conditions in MCI depends partly on the effective neuroprotective effect seen at an early phase of the disease.

Conclusions

There is substantial evidence that fragmented sleep, advanced sleep phase syndrome, insomnia, and impaired daytime alertness seen in advanced age are the result of brain dysfunction that is closely linked to disruptions in the regulation of circadian rhythms. There is also evidence that by addressing these problems directly significant improvements can be made in the quality of life experienced by the affected individuals.

Older subjects with sleep disorders frequently exhibit impairments in the circadian pacemaker and decreases of circulating melatonin levels, and therapy involving melatonin or melatonin analog administration not only improves their sleep onset and efficiency but also improves their health status and quality of life.

Undoubtedly, the aging process is multifactorial, and no single factor seems to be of basic importance. Although many theories relating melatonin to aging have been put forward, the role of this compound in the aging processes is not clear. However, there are several reasons to postulate a role for melatonin in aging:

- melatonin participates in many vital life processes and its secretion decreases gradually over the lifespan;
- melatonin is a potent free-radical scavenger, and the proposed link between oxidative stress and aging itself as well as age-related diseases suggest a role for melatonin in these processes;
- reduced concentrations of melatonin in the elderly may be related to lowered sleep efficacy very often associated with advanced age;
- reduced concentrations of melatonin may be related to deterioration of many circadian rhythms very often associated with advanced age; and
- melatonin exhibits immunomodulatory properties, and a remodeling of immune system function is an integral part of aging.

An example of the effect melatonin has on aging is that in AD and MCI patients. However, the question of whether melatonin has a therapeutic value in preventing or treating AD and MCI, affecting disease initiation or progression of the neuropathology and the driving mechanisms, remains to be investigated in future studies. Double-blind multicenter studies are urgently needed to further explore and investigate the potential and usefulness of melatonin as an antidementia drug. Its usefulness in symptomatic treatment, concerning sleep, sundowning or cognitive impairment, even in a progressed state, further underscores the need for such definitive studies.

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Part 2
Chapter
10

Neuroendocrine and homeostatic changes in the elderly

Sleep and diabesity in older adults

Eve Van Cauter and Rachel Leproult

Introduction: the epidemic of diabesity

The prevalence of obesity is increasing worldwide, particularly in the US [1]. Obesity is a major risk factor for type 2 diabetes mellitus (T2DM), and it is estimated that more than 20 million Americans are currently diabetic and that one third of them remains undiagnosed (Diabetes statistics from the American Diabetes Association available at: http://www.diabetes.org/diabetes-statistics.jsp, accessed April 28, 2006). A new term has been coined to describe the common clinical association of T2DM and obesity: "diabesity." As diabetes risk increases with age, the impact of the epidemic of obesity on the prevalence of diabetes is particularly important for adults in midlife and late life.

Nearly 25% of American adults between the age of 50 and 69 years were obese in 2001 as compared to approximately 15% in 1991. The epidemic of obesity has not spared the older segment of the population, as the proportion of obese individuals 70 years and older has increased from 11 % in 1991 to 17% in 2001. Food marketing practices (i.e. portion size, accessibility of inexpensive, calorie-dense fast food) and reduced physical activity are the most common lifestyle explanations for the epidemic of obesity but experts agree that they do not fully explain the magnitude and chronology of the secular changes in obesity prevalence.

One behavior that seems to have developed during the past few decades and has become highly prevalent, particularly amongst Americans, is sleep curtailment. In 1960, a survey study conducted by the American Cancer Society found modal sleep duration to be 8.0 to 8.9 hours [2] while in 2008, participants in the survey conducted by the National Sleep Foundation poll reported sleeping on average 6 hours and 40 minutes during weekdays [3]. Analyses of national data indicate that a greater percentage of adult Americans reported sleeping 6 hours or less in 2004 than in 1985 [4]. In 2004, more than 30% of adult men and women between the ages of 30 and 64 years reported sleeping less than 6 hours per night [4]. For adults 65 years and older, the proportion was 20% for men and more than 25% for women. In a recent study of early-middle-aged adults where sleep duration was measured objectively using wrist actigraphy [5], mean sleep duration was only 6.1 hours.

While factors other than voluntary bedtime curtailment undoubtedly contribute to shorter sleep in older adults, the fact that the proportion of short sleepers in the older age groups has increased substantially over the past two decades suggests that behavior plays a role. Interestingly, the decrease in average sleep duration in the USA has occurred over the same time period as the increase in the prevalence of obesity and diabetes.

Detailed reviews of the prevalence of sleep disorders in older adults have been presented in other chapters of this volume. The two most common sleep disorders in the elderly are sleep-disordered breathing (SDB) and insomnia. The prevalence of both types of sleep disorders has also increased with the epidemic of obesity as obesity is the major risk factor for SDB [6] and a substantial proportion of obese individuals suffer from insomnia [7]. Thus, the epidemic of obesity has been paralleled by an increased prevalence of *short sleep* and *poor sleep*.

The present chapter examines the existing evidence relating reduced sleep duration and quality – as occurs in a majority of older adults – and the epidemic of diabesity. In the first two sections, we describe how glucose regulation and the neuroendocrine regulation of appetite vary across the sleep–wake cycle in young and older adults. The following section discusses the impact of age-related alterations in sleep on hormonal function. The fourth and fifth sections summarize the laboratory and epidemiological studies that have provided evidence for an adverse impact of reduced sleep duration or quality on the risks of diabetes and obesity, respectively. We conclude with a

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brief discussion of the putative benefits of improving sleep duration and quality as a strategy for successful metabolic aging.

Glucose regulation and the sleep–wake cycle: impact of age

Blood levels of glucose are tightly regulated within a narrow range to avoid hypoglycemia and hyperglycemia as both conditions have serious adverse consequences. Glucose tolerance refers to the ability to metabolize exogenous glucose and return to baseline blood glucose concentrations. Glucose tolerance is dependent on the balance between glucose production by the liver and glucose utilization by insulin-dependent tissues, such as muscle and fat, and non-insulin dependent tissues, such as the brain. Glucose tolerance is critically dependent on the ability of pancreatic beta cells to release insulin (beta cell responsiveness) and on the ability of insulin to inhibit glucose production by the liver and promote glucose utilization by peripheral tissues (i.e. insulin sensitivity). Reduced insulin sensitivity, or insulin resistance, occurs when higher amounts of insulin are needed to dispose of the same amount of glucose. Glucose tolerance is also critically dependent on cerebral glucose uptake since the brain represents at least 40% of total glucose metabolism.

In normal individuals, glucose tolerance varies across the day such that plasma glucose responses to exogenous glucose are markedly higher in the evening than in the morning, and glucose tolerance is at its minimum in the middle of the night [8]. The reduced glucose tolerance in the evening is at least partly due to a reduction in insulin sensitivity concomitant with a reduction in the insulin secretory response to elevated glucose levels. The further decrease in glucose tolerance during the night is dependent on the occurrence of sleep. Indeed, a variety of mechanisms intervene to maintain stable glucose levels during the extended overnight fast associated with sleep [8]. Overall glucose utilization is greatest during wake and lowest during non-REM (stages 2, 3, and 4) sleep with intermediate levels during REM sleep [9]. In the first half of the night, glucose metabolism is slower, partly because of the predominance of slow wave sleep that is associated with a marked reduction in cerebral glucose uptake [10, 11], and may also be because of a reduction in peripheral glucose utilization. The release of growth hormone (GH) during early sleep contributes to prevent the decline of glucose levels. These effects are reversed during the second half of the night, when light non-REM sleep and REM sleep are dominant, GH is no longer released, and awakenings are more frequent.

To study variations in glucose tolerance across a 24-hour cycle, a constant glucose challenge, such as identical meals or snacks, identical loads of oral glucose or an intravenous infusion of glucose at a constant rate, must be used. The latter procedure allows for the assessment of glucose tolerance during sleep as well as during wake. Further, the infusion of glucose inhibits hepatic glucose production and variations in blood glucose concentrations then directly reflect variations in glucose utilization. Figure 10.1 shows the mean 24-hour profiles of plasma glucose, insulin secretory rates (ISR), and plasma GH from groups of healthy, overweight, older men (mean ± SD of age: 65 ± 5 years; mean ± SD of BMI: 28.6 ± 1.9 kg/m^2) compared to those of similarly overweight young men (mean ± SD of age: 25 ± 4 years; mean ± SD of BMI: 28.3 ± 3.3 kg/m^2) and lean young men (mean ± SD of age: 25 ± 2 years; mean ± SD of BMI: 21.6 ± 1.5 kg/m^2). The comparison of the glucose and insulin profiles across age groups illustrates the deterioration of glucose tolerance and the increased insulin resistance that are typical of aging. Levels of slow wave sleep (SWS) and nocturnal GH release were drastically decreased in the older subjects. The sleep-associated increase in glucose levels was dampened in the older subjects, consistent with the absence of the hyperglycemic effects of GH but also with the fact that low amounts of SWS likely resulted in lesser decreases in brain glucose utilization. Remarkably, in the older subjects, insulin secretion largely failed to increase in response to the sleep-associated glucose rise, demonstrating the existence of a clear reduction in beta cell responsiveness in aging. Thus, decreased glucose tolerance in aging is not only associated with insulin resistance but also with a relative insensitivity of the beta cell to the modulation of glucose regulation by sleep.

The impact of age on the 24-hour profiles of glucose, insulin, and counter-regulatory hormones is further illustrated in Figure 10.2. The subjects were healthy older and young adults (ages 50–69 years versus 20–28 years, BMI: 22–28 kg/m^2 versus 21–25 kg/m^2) who received three identical high-carbohydrate meals. Total sleep time, sleep efficiency, and amount of slow wave sleep were lower in the older group than in the young volunteers. The 24-hour profiles of glucose and

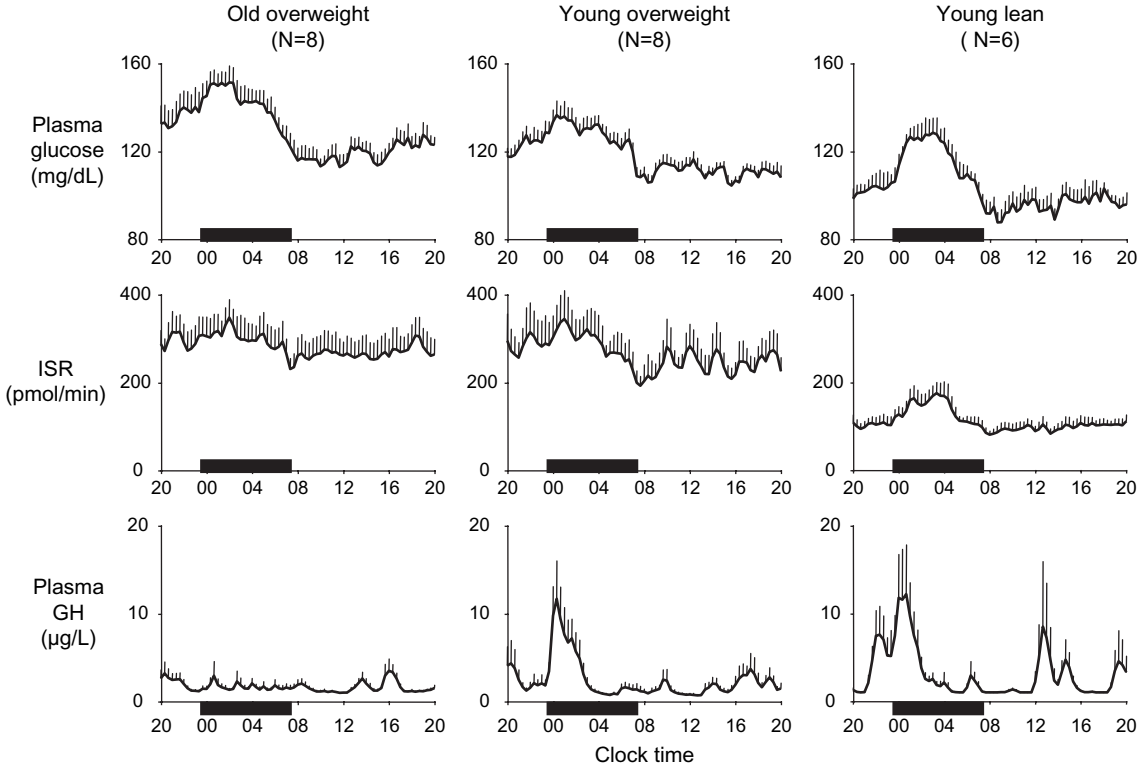

Figure 10.1. 24-hour profiles (mean + SEM) of plasma glucose (top panels), insulin secretory rates (middle panels), and plasma growth hormone (bottom panels) in overweight older adults (N=8, left panels), in overweight young adults (N=8, middle panels), and in lean young adults (N=6, right panels). Caloric intake consisted of a constant glucose infusion. The black bars represent the time allocated to sleep.

insulin (top panels) were similar in the two age groups with the older subjects showing a trend ($p = 0.056$) towards higher 24-hour mean glucose levels (105 ± 6 mg/dL) when compared with the young (98 ± 8 mg/dL). There was also a trend for higher insulin levels in older adults. When the profiles of Homeostatic Model Assessment (HOMA: insulin × glucose) values were calculated, this index of insulin resistance was elevated in older adults. Growth hormone levels were uniformly lower in the older subjects although a small sleep-related increase was still detectable. The amplitude of the 24-hour rhythm of plasma cortisol was dampened, mostly because of a failure to suppress hypothalamo-pituitary-adrenal (HPA) axis activity in the late evening and early part of sleep. A similar alteration of HPA regulation can be observed in young subjects submitted to partial or total sleep deprivation [12] and in insomniacs with reduced total sleep time [13]. Diurnal changes in epinephrine (E) and norepinephrine (NE) levels were present in both age groups with higher levels during the day and lowest levels during sleep. Consistent with the elevation of sympathetic nervous activity that is typical of aging, the older subjects had higher NE levels than the young throughout the 24-hour sleep–wake cycle, with the age difference being higher during sleep than during wake. The apparent higher E levels during sleep in older adults as compared to young volunteers failed to reach significance.

In summary, reduced sleep duration and quality in healthy older adults appear to be associated with – and perhaps partly responsible for – changes in GH, cortisol, E, and NE that could all adversely impact glucose tolerance and/or insulin sensitivity. Reduced sleep duration and quality are also likely to contribute to age-related declines in cerebral glucose utilization, particularly in the prefrontal cortex [14, 15].

Neuroendocrine regulation of appetite and the sleep–wake cycle: impact of age

Appetite is regulated by the interaction between metabolic and hormonal signals and neural mechanisms.

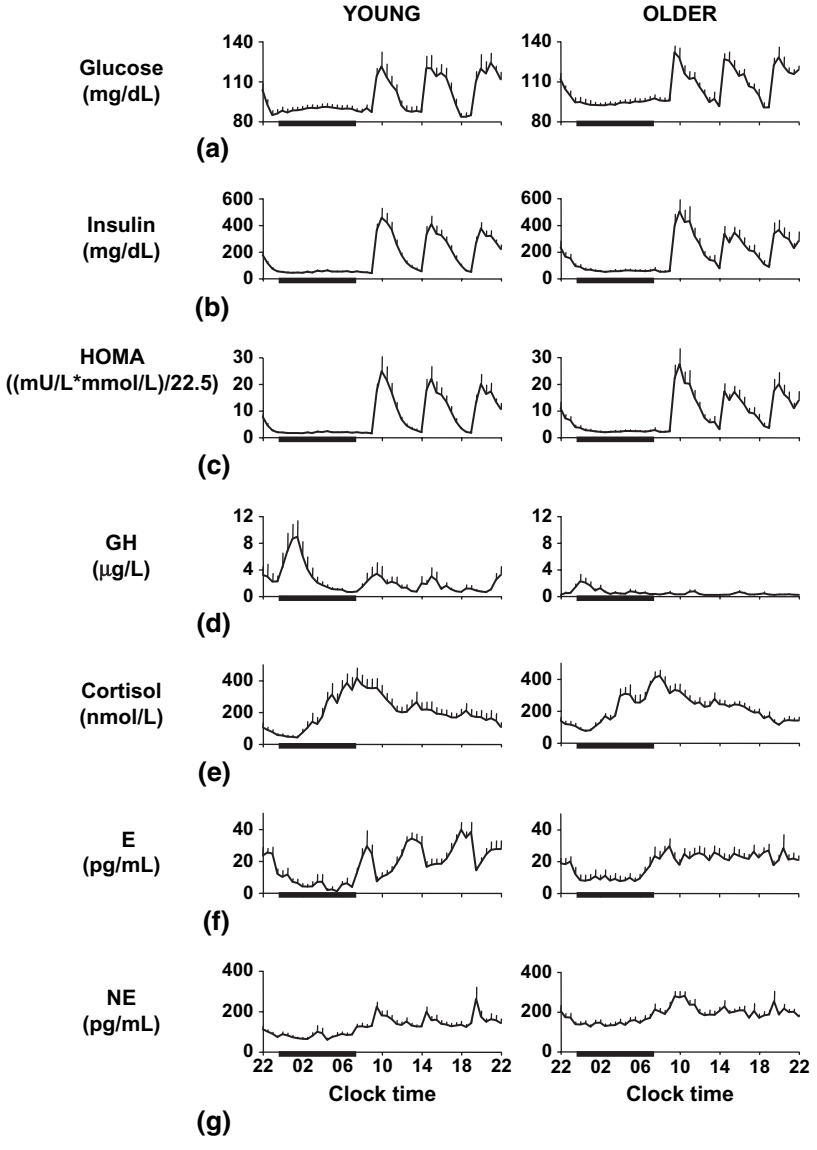

Figure 10.2. 24-hour profiles (mean + SEM) of (a) glucose, (b) insulin, (c) the Homeostatic Model Assessment (HOMA, product of glucose by insulin), (d) growth hormone, (e) cortisol, (f) epinephrine, and (g) norepinephrine in healthy young adults (left panels) and in healthy older adults (right panels). The subjects received three identical carbohydrate-rich meals. The black bars represent the time allocated to sleep.

The peripheral signals that affect appetite-regulating centers in the arcuate nucleus of the hypothalamus include leptin, an appetite-inhibiting hormone, and ghrelin, an appetite-stimulating hormone. The peripheral levels of leptin and ghrelin undergo large and consistent variations across the sleep–wake cycle, which is schematically illustrated in Figure 10.3. Leptin is primarily secreted by adipose tissue and promotes satiety [16]. Ghrelin is a peptide released primarily from the stomach and increases appetite and food intake [17]. In humans, plasma ghrelin levels are rapidly suppressed by food intake (particularly carbohydrate-rich foods) and then rebound after 1.5–2 hours, paralleling the resurgence in hunger. Thus, leptin and ghrelin exert opposing effects on appetite. As illustrated in Figure 10.3, under normal conditions, the 24-hour profile of human plasma leptin levels shows a marked nocturnal rise, which is dependent on meal intake [18]. However, a study using continuous enteral nutrition showed the persistence of a sleep-related leptin elevation during both nocturnal and daytime sleep [19]. The 24-hour profile of ghrelin levels also shows a nocturnal rise, which partly reflects the post-dinner rebound. Ghrelin levels spontaneously decrease in the second half of the sleep period, despite the maintenance of the fasting condition [20], suggesting that sleep may

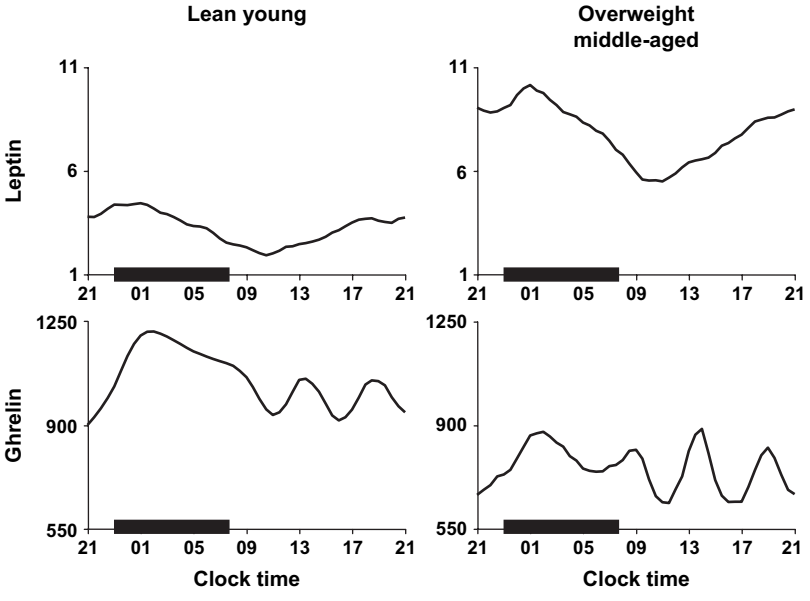

Figure 10.3. Schematic representation of 24-hour profiles of leptin (top panels) and ghrelin (bottom panels) levels under normal conditions including three identical meals in young lean (left panels) and overweight middle-aged (right panels). The black bars represent the sleep periods.

in fact inhibit ghrelin release. Elevated leptin levels in association with decreasing ghrelin levels during sleep may serve to suppress hunger during the overnight fast. Age and increased adiposity elevate leptin levels and suppress ghrelin levels but the diurnal variation is generally preserved (right panels of Figure 10.3).

The identification in 1998 of a small population of neurons that express two excitatory neuropeptides (orexin A and orexin B) that have potent wake promoting effects and stimulate food intake, particularly at a time when normal food intake is low, has provided a molecular link between sleep–wake regulation and the neuroendocrine control of appetite [21, 22]. Orexin neurons are mainly concentrated in the lateral hypothalamus and have excitatory projections to all the components of the ascending arousal system, and also project diffusely to the entire cerebral cortex [23]. The orexin system also activates the appetite-promoting neuropeptide Y neurons in the arcuate nucleus of the hypothalamus. Furthermore, orexin neurons have dense projections to the dopaminergic ventro-tegmental area (VTA) and nucleus accumbens (NA), which are important in the hedonic control of food intake [24, 25]. Thus, overactivation of the orexin system is likely to increase both hedonic and homeostatic feeding. Orexinergic activity is in turn influenced by both central and peripheral signals, with glucose and leptin exerting inhibitory effects while ghrelin promotes further activation [22].

Deficiencies in the orexin system are associated with sleep disorders involving chronic excessive daytime sleepiness, including narcolepsy and obstructive sleep apnea [26, 27]. In contrast, when sleep deprivation is enforced behaviorally rather than the result of a chronic pathological condition, the orexin system is overactive, as demonstrated by sleep deprivation studies in rats, dogs, and squirrel monkeys [28, 29, 30]. This overactivity of the orexin system during sleep deprivation may serve to maintain wakefulness against the increased sleep pressure but is also likely to be involved in increasing hunger and food intake.

Studies in senescent laboratory animals have indicated that aging may be associated with a decreased impact of orexin on food intake which could be responsible for reductions in appetite and food intake that are common in late life. A reduction in hypocretinergic innervation of basal forebrain nuclei of old hamsters and a lower concentration of orexin A in the cerebrospinal fluid of older rats has also been demonstrated. Taken together, these findings suggest that late life may be associated with an overall decrease in orexin system activity, which could contribute to weakening the waking drive and explain the increased daytime sleepiness and napping behavior of the elderly.

Age-related alterations in sleep: hormonal implications

There is increasing evidence that age-related alterations in sleep quality may result in disturbances of endocrine function, raising the hypothesis that some of the hormonal and

metabolic hallmarks of aging partly reflect the deterioration of sleep quality. In particular, hormones that affect determinants of glucose regulation and adiposity are profoundly affected by sleep duration and quality.

There is good evidence for a role of decreased SWS in the age-related decline of GH, a hormone that plays an important role in the control of body composition, with lower amounts of GH linked to higher adiposity and lower lean mass and vice versa. Sleep loss and poor sleep quality have been associated with increases in evening cortisol levels, an alteration that promotes insulin resistance.

Several studies have shown that decreases in amount of SWS occur rapidly in adulthood (30–40 years of age) and precede the appearance of significant sleep fragmentation or declines in REM sleep. Figure 10.4 illustrates the chronology of aging of SWS and REM sleep (upper panels) as compared to age-related changes in nocturnal GH release and evening cortisol concentrations (lower panels) from a retrospective analysis of sleep and concomitant profiles of plasma GH and cortisol in 149 normal, healthy, non-obese men, aged 16–83 years. It may be seen that the impact of aging on GH release occurred with a chronology similar to that of the decline in SWS, characterized by major decrements from early adulthood to midlife [31]. The statistical analysis further indicated that reduced amounts of SWS, and not age *per se*, are associated with reduced GH secretion in midlife and late life. The observation that, in older adults, levels of insulin-like growth factor (IGF-1), the hormone secreted by the liver in response to stimulation by GH, are correlated with the amounts of SWS [32], is consistent with this finding. The relative GH deficiency of the elderly is associated with increased fat tissue and abdominal obesity, reduced muscle mass and strength, and reduced exercise capacity. The persistence of a consistent relationship between SWS and GH secretion in older men suggests that drugs that reliably stimulate SWS in older adults may represent a novel strategy for GH replacement therapy. In contrast to the rapid decline of SWS and GH secretion from young adulthood to midlife, the impact of age on REM sleep does not become apparent until later in life and the age-related elevation of evening cortisol levels follows the same chronology (right panels of Figure 10.4) [31]. Analysis of variance indicates that low amounts of

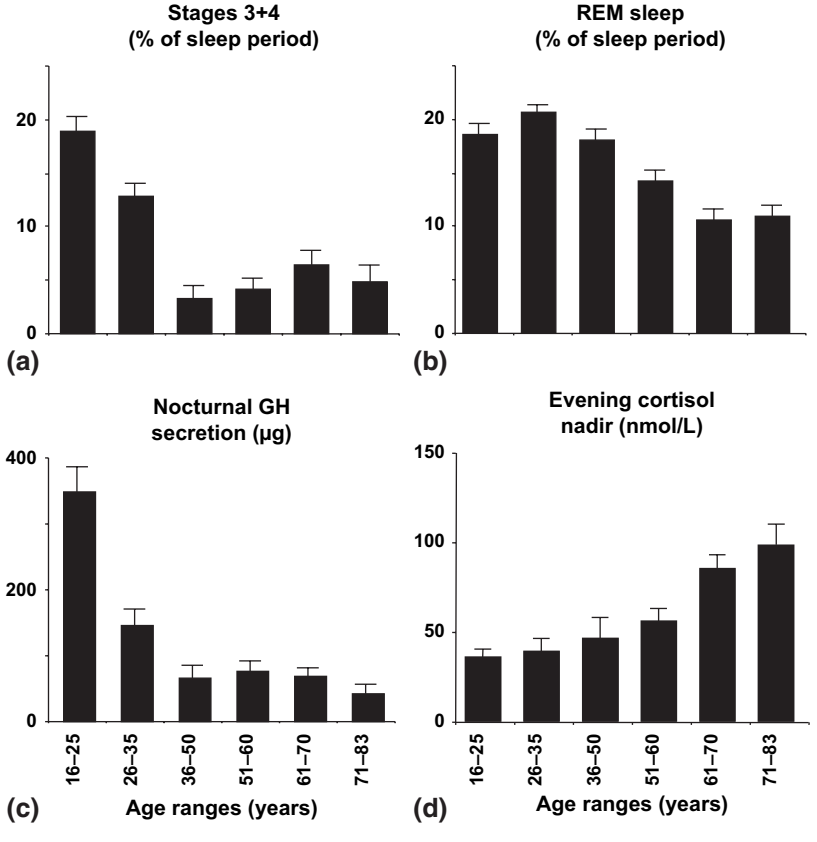

Figure 10.4. Chronology of aging (mean + SEM in each age range) of (a) percentage of slow wave sleep (stages 3+4), (b) percentage of REM sleep, (c) amount of growth hormone secreted during the night-time, and (d) evening cortisol nadir.

REM sleep were a significant predictor of the elevated cortisol nadir, after controlling for age and BMI. Both animal and human studies have indicated that deleterious effects of HPA hyperactivity are more pronounced at the time of the trough of the rhythm than at the time of the peak. Therefore, modest elevations in evening cortisol levels could facilitate the development of insulin resistance [33], and further promote sleep fragmentation. Indeed, several studies have demonstrated that elevated corticosteroid levels result in increased propensity for awakenings [34, 35].

Impact of reduced sleep duration and quality on diabetes risk

We briefly review below the laboratory and epidemiological evidence supporting the hypothesis that reduced sleep duration and quality may be novel risk factors for type 2 diabetes. While published laboratory studies have involved only young adults, the findings are nonetheless highly relevant to the well-documented age-related decreases in total sleep time and amount of SWS.

Laboratory studies

Our group published the first laboratory study designed to address the metabolic and hormonal consequences of recurrent partial sleep restriction [36]. Eleven young, healthy men were studied after 6 days of sleep restriction with 4-hour bedtimes followed by 7 days of sleep recovery with 12-hour bedtimes [36, 37, 38]. Examination of glucose metabolism included a frequently sampled intravenous glucose tolerance test (ivGTT) administered in the morning of the fifth day of each bedtime condition. This test allows for the simultaneous evaluation of beta cell responsiveness (acute insulin response to glucose; AIRg), insulin sensitivity (SI), and glucose effectiveness (Sg; a measure of non-insulin-dependent glucose utilization). A mathematical model referred to as "the minimal model" is fitted to the simultaneous glucose and insulin values to extract AIRg, SI, and Sg. In individuals with normal glucose tolerance, the product AIRg × SI, termed disposition index (DI), remains constant because their beta cell function is able to compensate for insulin resistance with increased insulin release. Type 2 diabetes occurs when beta cell function is unable to be sufficiently upregulated to compensate for insulin resistance, resulting in hyperglycemia. Thus low DI values represent a higher risk of type 2 diabetes. The results of the ivGTT are summarized in the upper part of Table 10.1. AIRg was reduced by more than 30% in the state of sleep debt even though SI tended to decrease. Sg was also significantly decreased. As a result, the DI was decreased by an average of 40% in the state of sleep debt as compared to the fully rested state. This large decrease in DI was of clinical significance since 3 of the 11 subjects had a DI<1000 at the end of the sleep debt period, indicative of a very high risk of diabetes. We subsequently confirmed the deleterious impact of sleep restriction on glucose metabolism in a follow-up study using a randomized cross-over design [38]. Recently, our findings were confirmed by an independent group that used the hyperinsulinemic euglycemic clamp to assess insulin sensitivity in healthy men after 1 week of sleep restriction to 5 hours per night and demonstrated a significant reduction in SI [39].

Table 10.1. ivGTT findings in a protocol of reduced sleep duration (upper part) and in a protocol of reduced sleep quality (lower part)

	Fully rested	After sleep intervention	*p* level
After 5 nights of 4 hours in bed *n* = 11 (all men)			
Sg (% per minute)	2.6 ± 0.2	1.7 ± 0.2	<0.0005
AIRg (mU/L. min)	566 ± 144	403 ± 125	0.04
SI (mU/L. min)	7.10 ± 1.04	5.19 ± 0.51	0.15
Disposition index (DI)	3123 ± 537	1724 ± 343	0.003
After 3 nights of SWS suppression *n* = 9 (4 women)			
Sg (% per min)	2.4 ± 0.3	1.9 ± 0.2	0.18
AIRg (mU/L. min)	314 ± 41	323 ± 36	0.73
SI (mU/L. min)	8.4 ± 1.1	5.9 ± 0.7	0.009
Disposition index (DI)	2347 ± 299	1745 ± 144	0.02

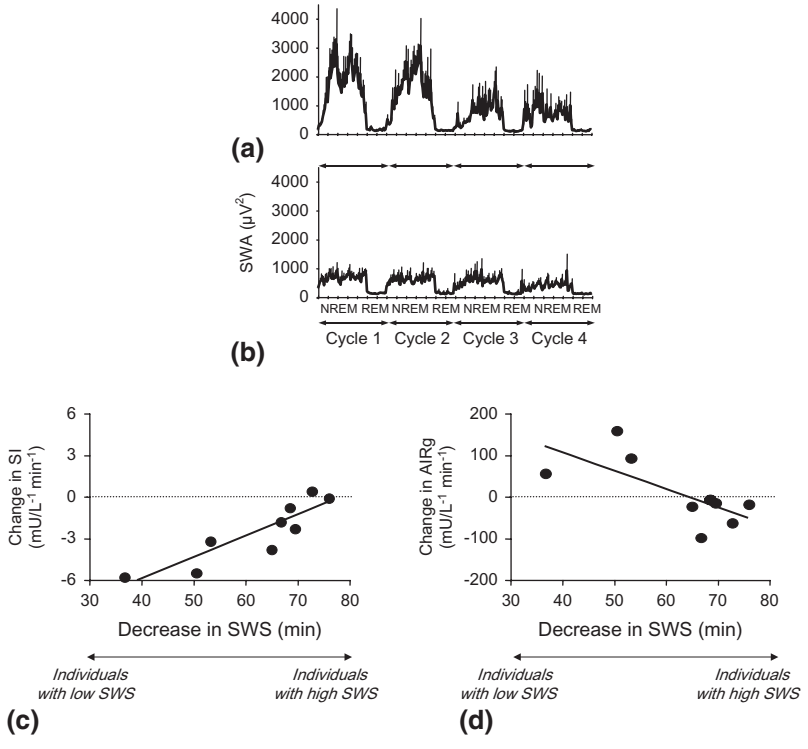

Figure 10.5. Results from the slow wave sleep (SWS) suppression study [40]. (a,b) The profiles (mean + SEM) of slow wave activity (SWA) for the first four normalized NREM/REM cycles during an undisturbed night (a) and during the third night of SWS suppression (b). SWA was calculated as the EEG spectral power in the 0.5–4 Hz frequency range. (c,d) The relationship between the changes in SWS, and the changes in insulin sensitivity and in acute insulin response to glucose, respectively, after 3 nights of SWS suppression. The individual with low SWS during baseline, before SWS suppression, ended up with extremely low amount of SWS after the intervention. Those subjects had also the biggest decrease in insulin sensitivity (c) without sufficient compensation in acute insulin secretion (d).

Normal aging is associated with a marked reduction in SWS and with an increased risk of diabetes. A recent study tested the hypothesis that a decrease in SWS could have an adverse impact on diabetes risk, in the absence of any other age-related condition [40]. The study achieved a selective suppression of SWS without change in sleep duration by delivering acoustic stimuli of varying frequencies and intensities to amplifiers located on each side of the bed. The sounds were calibrated in order to suppress delta activity while avoiding a full arousal. Nine healthy young volunteers were each tested under two conditions, in randomized order (1) after two consecutive nights of undisturbed "baseline" sleep, and (2) after three nights of suppression of SWS were achieved. Glucose regulation was assessed by ivGTT at the end of each condition. The amount of SWS was decreased by nearly 90% without any change in total sleep time, or in the duration of REM sleep. This decrease in SWS is similar to that which occurs over the course of four decades of normal aging. The upper part of Figure 10.5 illustrates the impact of the experimental intervention on levels of SWA. SWA was markedly reduced while spectral EEG power in other frequency bands including theta, alpha and sigma was unaffected. The findings from the ivGTT are summarized in the lower part of Table 10.1. After three nights of suppression of SWS, insulin sensitivity (SI) was decreased by ~25%. The magnitude of the change in SI was comparable to that associated with a difference in weight of 8–13 kg. The decrease in SI associated with the reduction of SWS was not compensated for by an increase in insulin release, as AIRg remained virtually unchanged. Consequently, the DI was ~20% lower after SWS suppression.

Importantly, as shown in the lower part of Figure 10.5, the magnitude of changes in SI and AIRg was correlated with the magnitude of the reduction in SWS. The individuals who had low levels of SWS at baseline had the largest decrements in insulin sensitivity without adequate compensatory increases in AIRg. This indicates that older adults are likely to be at a greater risk of diabetes when sleep quality further deteriorates. There were no correlations between the measures of sleep fragmentation and the decrease in SI, suggesting that the alterations observed after SWS suppression are unlikely to be related to a decrease in sleep continuity.

Epidemiological studies

At least seven studies have examined the cross-sectional analyses of the association between sleep duration and quality and the prevalence of diabetes (reviewed in

[41]). In this chapter, we will focus on prospective studies because they provide some evidence regarding the direction of causality. Tables 10.2 and 10.3 summarize the prospective studies that have related, respectively, sleep duration and sleep quality to diabetes risk. This literature review was completed in October 2008. For sleep duration, four of the six studies found an association between being a short sleeper and having an increased risk of developing diabetes. For sleep quality, five out of six studies had positive findings. All the studies relied on self-reported sleep and it may be argued that poor sleep quality may lead to a misperception of time spent asleep. In sum, the bulk of the epidemiological evidence from prospective studies is consistent with the laboratory work in supporting a causal link between reduced sleep duration and/or quality and increased risk of T2DM.

Impact of reduced sleep duration and quality on obesity risk

Assessment of leptin and ghrelin levels

To date, four published laboratory studies have examined the impact of recurrent partial sleep restriction (2–14 days) on the neuroendocrine regulation of appetite. In a preliminary study published in 2003, Guilleminault *et al.* assessed leptin levels at six time points of the 24-hour cycle in volunteers studied after 7 days of sleep restriction to 4 hours per night and reported a significant decrease in peak leptin levels [51]. Two studies published in 2004 confirmed and extended these findings. One study compared the 24-hour profiles of plasma leptin levels obtained after sleep restriction (6 days of 4 hours in bed), after sleep extension (6 days of 12 hours in bed) and after regular bedtimes (2 days of 8 hours in bed) in the same volunteers. A remarkable "dose–response" relationship between sleep length and characteristics of the leptin profile was observed [37]. Indeed, the overall mean leptin concentration, the level of the nocturnal acrophase and the amplitude of the diurnal variation gradually increased from the 4-hour to the 12-hour bedtime condition.Importantly, these differences in 24-hour regulation of leptin levels between the three bedtime conditions occurred despite identical amounts of caloric intake and similar low levels of physical activity, as well as stable BMI. Of note, the reduction in mean peak leptin (26%) between the 4 hours and the 12 hours in bed condition was similar to

Table 10.2. Prospective studies linking short sleep duration and risk of type 2 diabetes

Citation	Follow-up	Population/setting	N	Key findings
Studies that support an association				
Ayas *et al.* 2003 [42]	10 years	Female nurses ages 30–55 years	70026	15–30% increased risk of incident diabetes associated with sleep duration ≤6 hours relative to 7–8 hours but no longer significant after adjusting for BMI. Symptomatic diabetes remains significant after adjusting for BMI
Mallon *et al.* 2005 [43]	12 years	Random sample of the middle-aged Swedish population	2663	Difficulties in maintaining sleep or sleep duration ≤5 hours are associated with an increased incidence of diabetes in men but not women
Yaggi *et al.* 2006 [44]	15–17 years	Massachusetts Male Aging Study	855	Compared with those reporting sleep duration of 7 hours/night, men reporting short sleep duration (≤6 hours/night) were twice as likely to develop diabetes (RR: 1.95; 95% CI: 0.95–4.01)
Gangwisch *et al.* 2007 [45]	10 years	Participants in the NHANES I study	8992	Participants reporting short sleep duration (<5 hours per night) were significantly more likely to have incident diabetes during the 10-year follow-up
Studies that did not support an association				
Bjorkelund *et al.* 2005 [46]	32 years	Swedish women ages 38–60 years	661	No association between hours of sleep and incident diabetes
Hayashino *et al.* 2007 [47]	4.2 years	High-risk and Population Strategy for Occupational Health Promotion Study (HIPOP-OHP)	6509	Sleep duration did not predict incidence of diabetes

Table 10.3. Prospective studies linking poor sleep quality and risk of type 2 diabetes

Citation	Follow-up	Population/setting	N	Key findings
Studies that support an association				
Kawakami *et al.* 2004 [48]	8 years	Japanese men	2649	High frequency of difficulty initiating or maintaining sleep is associated with an increased age-adjusted risk of developing type 2 diabetes
Nilsson *et al.* 2004 [49]	7–22 years	Swedish men aged 35–51	6599	Increased risk of incident diabetes among those who reported difficulty falling asleep or use of sleeping pills at baseline
Mallon *et al.* 2005 [43]	12 years	Random sample of the middle-aged Swedish population	2663	Difficulties in maintaining sleep or short sleep duration are associated with an increased incidence of diabetes in men but not women
Meisinger *et al.* 2005 [50]	11 years	MONICA surveys, Germany	8269	Difficulty maintaining sleep significantly associated with higher risk of T2DM post adjustment. Difficulty initiating sleep was not associated with T2DM in adjusted models
Hayashino *et al.* 2007 [47]	4.2 years	High-risk and Population Strategy for Occupational Health Promotion Study (HIPOP-OHP)	6509	Medium and high frequency of sleep initiation disturbance was associated with an increased risk of developing diabetes
Studies that did not support an association				
Bjorkelund *et al.* 2005 [46]	32 years	Swedish Women – population-based sample	661	Sleep problems at baseline (1968; duration & quality) did not increase risk of developing diabetes over 32- year follow-up

what has been reported in healthy volunteers fed only 70% of their energy requirement during 3 consecutive days, i.e. a caloric restriction by nearly 1000 calories per day. In a randomized cross-over design study of normal young adults after 2 nights of 4 hours in bed versus 2 nights of 10 hours in bed, the daytime leptin and ghrelin profiles were assessed simultaneously and the subjects completed validated scales for hunger and appetite for various food categories at hourly intervals. Caloric intake was strictly controlled in the form of an intravenous glucose infusion at a constant rate calculated to match normal caloric requirements. In the short sleep condition as compared to the long sleep condition, overall leptin levels were decreased by an average of 18%, while ghrelin levels increased by 24%, and the ghrelin:leptin ratio increased by more than 70%. Hunger showed a 23% increase and appetite for calorie-dense foods with high carbohydrate content was increased by more than 30% [52]. Importantly, the increase in ghrelin:leptin ratio accounted for nearly 70% of individual variability in increased hunger [52]. If the observed increase in hunger ratings during sleep restriction were to translate into an increase in food intake, significant weight gain would occur over time. A recent study of overweight, middle-aged adults studied in the laboratory during 2 weeks of sleep extension (+1.5 hours per night) as compared to 2 weeks of sleep restriction (−1.5 hours per night) in a randomized cross-over design has indeed shown an increased food intake from snacks during the short sleep condition [53]. The participants remained in the sedentary environment of the laboratory and were exposed to unlimited amounts of palatable food during both sleep conditions. Weight gain occurred under both sleep conditions and profiles of leptin and ghrelin assessed at the end of each 14-day study did not differ according to time in bed.

Figure 10.6 summarizes the findings of all the studies (laboratory based and epidemiological) that have so far examined the impact of sleep loss on leptin and ghrelin levels. Two large epidemiological studies have shown an elevation of leptin level in a single morning blood sample, after controlling for BMI or adiposity, in habitual short sleepers [54, 55]. In the larger study [54], the level of ghrelin was also measured and was found to be positively associated with short sleep [54]. A recent study examined the effects of one night of sleep restriction (4.5 hours vs. 7 hours) and showed an increase in ghrelin but no change in leptin [56]. A subsequent smaller study involving only post-menopausal women did not confirm the link between sleep duration, BMI, and leptin and ghrelin

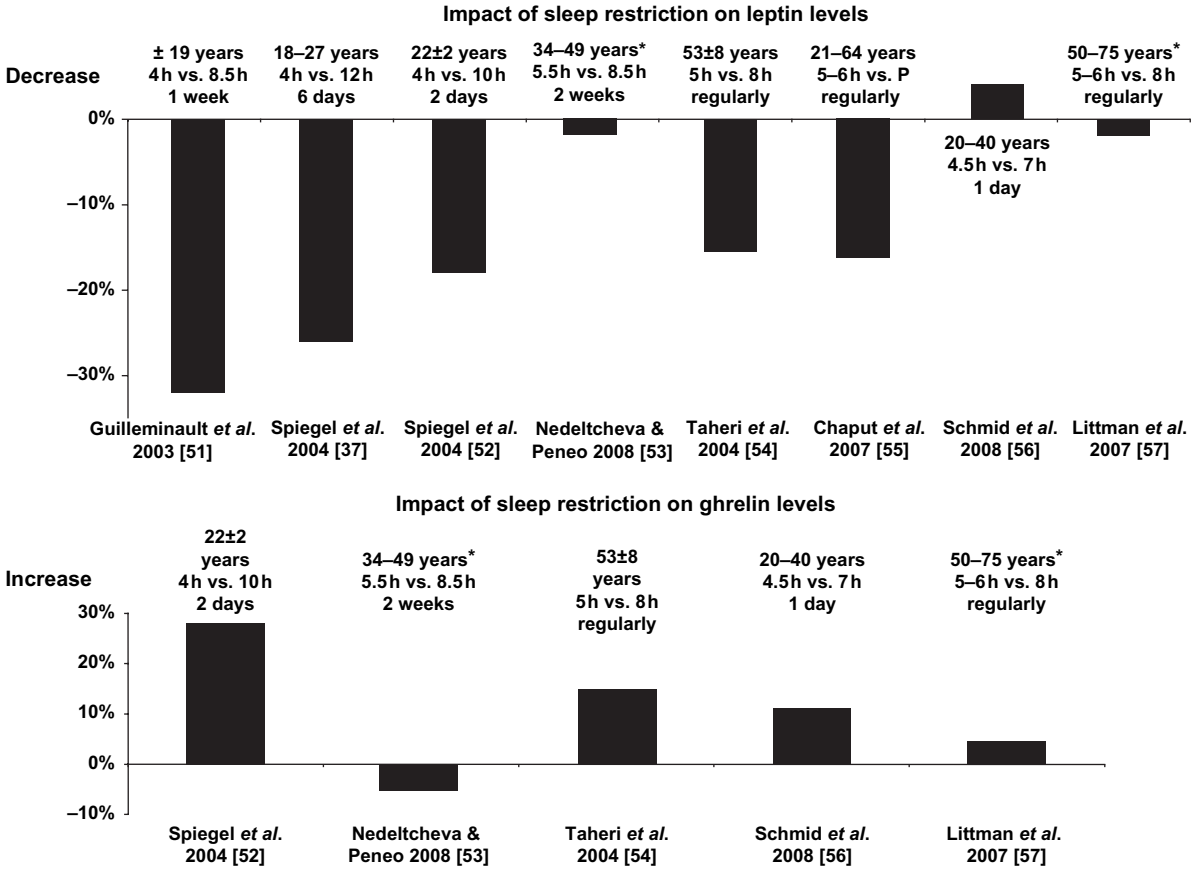

Figure 10.6. Percentages of changes due to sleep restriction in leptin (top panel) and in ghrelin (bottom panel) levels – laboratory and epidemiological studies.

*indicates that the subjects studied were overweight.

levels [57]. Difference in age of the sample may play a role in the divergent findings as orexigenic signals are generally thought to be weaker in older adults.

Epidemiological studies

An ever-growing number of cross-sectional epidemiological studies (numbering 52 as of September 2008) have provided evidence of an independent link between short and/or poor sleep and the risk for obesity. A recent meta-analysis including more than 600 000 adults and 30 000 children worldwide attempted to quantify the link between short sleep and obesity risk. The pooled odds ratio (OR) linking short sleep to obesity was 1.89 (95% CI: 1.46–2.43; $p < 0.0001$) in children and 1.55 (95% CI: 1.43 to 1.68; $p < 0.0001$) in adults [58]. An independent recent review similarly concluded that short sleep duration appears independently associated with weight gain, particularly in younger age groups [59].

Out of the six prospective studies that investigated the impact of short sleep on obesity risk in adults, three reported that shorter sleep durations are associated with an increased risk for overweight and obesity over the follow-up period [60]. Two of the three negative studies had very short follow-up periods, i.e. 2 years [61] and 5 years [62].

In summary, the body of epidemiological evidence has supported the hypothesis that sleep curtailment may be one of the more plausible "non-traditional" lifestyle factors contributing to the epidemic of obesity [63]. Increasing sleep duration for short sleepers has been suggested as a means to improve the health of the population as a whole [64]. Critics have argued that the effect size of short sleep (≤5 hours) in longitudinal studies involving a 10-year follow-up is small (with short sleepers gaining an excess weight ranging from 1 to 7 kg) [65]. Yet, the difference in weight gain between short and normal sleepers is well within the range of

weight loss that can be achieved with pharmacological interventions.

A limitation of nearly all epidemiological studies examining the relationship between sleep duration and BMI is that they were based on self-report sleep and did not simultaneously assess sleep quality. Thus, it remains to be determined whether short sleep in obese individuals is the result of bedtime curtailment or is due to the presence of a sleep disorder. Two recent reports have contributed to clarify this issue. First, a large-scale study [7] where participants reported sleep duration as well as subjective sleep disturbances (insomnia, excessive daytime sleepiness, sleep difficulty) and a measure of chronic emotional stress concluded that self-reported short sleep in obese adults may be a surrogate marker of subjective sleep disturbance and psychosocial stress [66]. This hypothesis is consistent with the existence of a "vicious circle" where short sleep may initially promote weight gain and the resulting excess adiposity would then induce sleep disturbances and psychological stress, with a net further decrease in total sleep time. Second, the cross-sectional association between sleep duration and obesity in a large number of older adults (3055 men: 67–96 years; 3052 women: 70–99 years) has been examined using wrist actigraphy for an average of 5.2 nights in all participants. Remarkably strong associations between objectively assessed short sleep and BMI emerged after controlling for multiple risk factors and medical conditions. For older adults who sleep less than 5 hours compared to those who sleep 7–8 hours, the odds of obesity (BMI >30 kg/m^2) was 3.7-fold greater in men and 2.3-fold greater in women. These associations persisted after adjusting for sleep apnea, insomnia, and daytime sleepiness.

Taken together, the epidemiological evidence suggests that reduced sleep duration and reduced sleep quality may both be novel risk factors for weight gain and obesity.

Conclusions

There is increasing evidence to indicate that the decreases in sleep duration and quality and the increased incidence of sleep disorders that occur in the course of aging are likely to play a role in the senescence of the endocrine system and in the development and severity of age-related metabolic disorders, including type 2 diabetes. Conversely, metabolic disorders may contribute to impair sleep quality, resulting in a "vicious cycle" linking sleep–wake regulation and metabolism in aging. Strategies to improve sleep quality may have beneficial metabolic and endocrine effects in older adults by delaying the development or reducing the severity of age-related metabolic disorders.

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Part 3 Sleep disorders in the elderly

Part 3
Chapter
11

Sleep disorders in the elderly

Assessment and differential diagnosis of sleep disorders in the elderly

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Introduction

Difficulties with sleep are common complaints amongst elderly patients, with up to 50% describing chronic sleep problems. Although a number of normal, age-related changes in sleep occur, problems with sleep are not an inevitable part of aging as many of these complaints are related to specific sleep disorders, circadian rhythm changes, medical or psychiatric illness, or the medications administered to treat these illnesses. This chapter will review the assessment and differential diagnosis of sleep disorders in the elderly.

Age-related changes in sleep

Elderly patients report a variety of difficulties with sleep including sleeping less despite spending more time in bed, waking more often during the night, waking up earlier in the morning, taking more naps, and taking longer to fall asleep than younger adults. Research has verified these subjective complaints objectively with polysomnography (PSG). A meta-analysis that included more than 3000 healthy subjects identified age-related changes in PSG parameters [1]. Beginning at 60 years of age, sleep efficiency (defined as the ratio of total sleep time to nocturnal time in bed) decreases and with further increases in age, continues to decline. Other sleep parameters were found to remain relatively stable, e.g. the amount of slow wave sleep begins to decrease in the third or fourth decade and then remains constant. The sleep of elderly patients is more fragmented, however, with an increase in the number of awakenings, arousals, and shifts in sleep stage, all of which result in lower sleep efficiency.

With age, the ability to sleep at night diminishes, often resulting in inadequate sleep. Insufficient sleep should not be considered a benign condition as it is associated with significant morbidity and increased mortality. Patients with sleep complaints report decreased quality of life and more symptoms of depression and anxiety when they are compared with those patients who sleep well. Sleep problems in the elderly may be especially hazardous as troubles with sleep are associated with an increased risk of falls and difficulty with ambulation, balance, and vision, even after controlling for medication use [2]. Cognitive deficits, specifically in the areas of attention, short-term memory, response times, and performance level, can be due to chronic sleep difficulties at any age and may be especially problematic for those elderly who are most vulnerable, i.e. those with underlying cognitive dysfunction at baseline. Sleep difficulties in the elderly are also associated with an increased risk in mortality as lower sleep efficiency (<80%) has been reported to almost double the risk of all-cause mortality [3].

While these normal age-related changes may explain an elderly patient's complaints about sleep, there are also a variety of other diagnoses that must be considered, including the presence of specific sleep disorders, circadian rhythm disturbances, and medical and psychiatric co-morbidities.

Specific sleep disorders

Sleep disordered breathing

Sleep disordered breathing (SDB) is a broad term used to describe a range of periodic respiratory events that occur during sleep, from simple snoring at the milder end to complete cessation of airflow (apnea) at the more severe end of the spectrum. The number of apneas and hypopneas (partial reduction in airflow) per hour of sleep is called the apnea–hypopnea index (AHI) and a diagnosis of SDB is made when a patient has an AHI ≥5–10.

Sleep disordered breathing is more common in older adults than younger adults with most longitudinal and cross-sectional studies finding that the prevalence increases or stabilizes with age [4, 5]. While the reported prevalence of SDB among middle-aged adults is approximately 4–9% [6], it has been reported to be 45–62% in adults over the age of 60 years [4]. In

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one longitudinal study [7], the prevalence of SDB did not increase with age and rather only changed with associated increases in body mass index. In another study [8], the prevalence of SDB did increase with increasing age (60–90 years). Reporting prevalence rates of SDB by 10-year age groups, the Sleep Heart Health Study [9] found increasing rates with increasing age only for those subjects with an AHI ≥15.

Risk factors for SDB in the elderly include increasing age, gender, family history/genetic factors, race, smoking, craniofacial anatomy, and obesity [10]. The use of sedating medications and alcohol consumption may increase a patient's risk.

As in younger adults, snoring and excessive daytime sleepiness (EDS), resulting from recurrent night-time arousals and sleep fragmentation, are the principal symptoms of SDB in the elderly. Excessive daytime sleepiness, often manifested as falling asleep at inappropriate times during the day and/or unintentional napping, can lead to social/occupational difficulties and cognitive dysfunction, which may be of particular importance for those patients with underlying cognitive impairment at baseline [11]. There are also several less common presentations of SDB that can be found in the elderly, which include complaints of insomnia, nocturnal confusion, and daytime cognitive impairment such as short-term memory loss and poor concentration.

Undiagnosed or untreated SDB is associated with considerable morbidity. The body of literature reporting negative consequences and associated conditions related to SDB, including hypertension, cardiac arrhythmias, congestive heart failure, myocardial infarction, and stroke, continues to grow. Much of this research, however, has focused on younger or middle-aged adults, and it is somewhat difficult to extrapolate the findings to older adults. Therefore, the exact relationship between SDB and these various morbid conditions in the elderly remains unknown.

In contrast, the negative effect of severe SDB (AHI ≥30) on cognition in the non-demented elderly patient is well established, with consistent reports of decreased attention, poor recall, slowed response time, and trouble completing executive tasks [12]. The relationship between milder SDB and cognition is less clear with some studies reporting that those patients with milder SDB (defined as AHI 10–20) may only have evidence of cognitive difficulties if they are excessively sleepy [13].

Accurate evaluation and assessment of elderly patients with suspected SDB requires a complete sleep history focused on the symptoms of SDB, the existence of other sleep disorders, and sleep-related habits in the presence of a bed partner or care-giver when possible. A thorough review of the patient's current and past medical and psychiatric history should also be completed, with particular attention paid to SDB-associated medical conditions, medications, the use of alcohol, and evidence of cognitive dysfunction. An overnight sleep recording should be performed to confirm the diagnosis. It should be noted that obtaining an overnight sleep study in an elderly patient may present some unique challenges including difficulties with transportation, resistance to spending the night in an unfamiliar environment, and trouble understanding complicated instructions. Anticipating some of these potential difficulties and involving the patient's bed partner or care-giver may help to resolve some of these issues.

Experts in the field continue to discuss whether SDB in the elderly is a distinct pathological condition, i.e. one that is different than that found in younger or middle-aged adults. While the answer to this question may help target new therapies, from a clinical standpoint, the answer seems less germane. If an older patient presents with symptoms and/or related consequences of SDB (i.e. EDS, cognitive dysfunction, stroke, etc.), then they should be treated, regardless of age [14].

Periodic limb movements in sleep/restless leg syndrome

Periodic limb movements in sleep (PLMS) is a disorder commonly found in elderly patients and is characterized by clusters of repetitive leg jerks or kicks during sleep. These leg movements typically occur every 20–40 seconds and recur throughout the night. The etiology of PLMS is unknown.

As each jerk or kick may result in an arousal or brief awakening, patients with PLMS have fragmented and disrupted sleep and therefore may present with complaints of EDS or unrefreshing sleep. Patients may or may not be aware of the leg kicks and may subjectively interpret the disrupted sleep that results as insomnia and instead complain of difficulty falling or staying asleep. The patient's bed partner may be bothered by the repetitive movements and can be helpful during the patient's assessment. The diagnosis of PLMS requires an overnight PSG showing a calculated periodic limb movement index (PLMI; the number of limb movements per hour of sleep) greater than or equal to five.

The prevalence of PLMS increases dramatically with age, with rates of up to 45% in community-dwelling adults, equally among men and women over the age of 65 [15]. Although the prevalence does increase with age, research has found that the severity of PLMS remains stable and does not worsen with increasing age [16].

Restless leg syndrome (RLS) is a condition strongly associated and often co-morbid with PLMS. This disorder is characterized by leg dysesthesia that occurs when the patient is in a relaxed awake or restful state, more commonly during the evening or at night. Patients typically describe an uncomfortable sensation in their legs accompanied by the urge to move. A variety of expressive and often colorful terms may be used to convey the unpleasant sensation that patients experience including creep-crawly, crazy legs, ants crawling, or pain. One essential clinical feature of RLS is that movement relieves the uncomfortable sensation temporarily. Like PLMS, the etiology of RLS is also unknown although it is associated with iron deficiency states (including pregnancy), uremia, peripheral neuropathy, and radiculopathy.

While the diagnosis of PLMS requires testing with polysomnography, patients with RLS can be diagnosed on the basis of history alone. Table 11.1 outlines the four essential features of RLS, according to the International Restless Legs Syndrome Study Group [17]. Patients with suspected RLS should also have evaluations of serum ferritin and percent iron saturation as low–normal ferritin (<45–50 µg/L) is associated with increased severity and risk of recurrence of RLS [18, 19].

The prevalence of RLS increases significantly with age, with rates in older adults reported to range from 9% to 20%, and women are affected twice as often as men [20, 21]. Given the close association between RLS and PLMS, there has been significant debate amongst sleep experts as to whether PLMS without RLS represents a diagnosable disorder, and, currently, there is no clear consensus. Research aimed at clarifying this condition is ongoing.

Table 11.1. Four essential questions required to make the diagnosis of RLS [17]

1. Do you experience the urge to move your legs (and/or other parts of your body), accompanied or caused by an uncomfortable and/or unpleasant sensation in the body part affected?
2. Does the urge to move or the uncomfortable/unpleasant feeling start and/or worsen during periods of rest, relaxation, or inactivity?
3. Is the urge to move or uncomfortable/unpleasant feeling partially or totally relieved by movement?
4. Does the urge to move or the uncomfortable sensation worsen in the evening or at night (as compared to the daytime) or does it only occur in the evening or at night?

Rapid eye movement (REM) sleep behavior disorder

REM sleep behavior disorder (RBD) is a condition in which the skeletal muscle atonia normally found in REM sleep is intermittently absent. Patients with this sleep disorder are therefore able to "act out their dreams" and typically display elaborate and complex movements such as punching, jumping/running out of bed, kicking, and/or yelling during REM sleep. These actions, which usually occur during the second half of the night when REM is more prevalent, generally correlate with vivid dream imagery, which is often recalled upon awakening. The patient's aggressive and/or violent behavior can result in unintended injuries to the patient and/or the patient's bed partner.

Although the precise etiology of RBD is unknown, it appears to be strongly related to a number of underlying neurological or neurodegenerative disorders including the synucleinopathies. Approximately 40% of RBD cases are associated with one of these conditions including Parkinson's disease and diffuse Lewy body disease. Research has found that RBD may actually be the first manifestation and harbinger of the presence of a neurodegenerative disease and may precede the onset of clinical neurological symptoms by years [22, 23]. Olson and colleagues [24] reported that 50% of patients diagnosed with idiopathic RBD developed Parkinson's disease or multiple system atrophy within 3–4 years, while Schenck and colleagues [22] found that after an initial diagnosis of RBD, 38% of men developed Parkinson's disease in a mean of 3.7 years. In addition, RBD is associated with narcolepsy.

Rapid eye movement sleep behavior disorder is more common in the elderly, and is especially prevalent in older men with reports that up to 90% of cases occur in this subset of older adults [24]. The overall estimated prevalence is reported to be 0.5%, with the highest incidence occurring after the age of 50 years [25].

As with the other specific sleep disorders, the diagnosis of RBD requires a thorough sleep history in the presence of the patient's bed partner if possible. A recent

screening questionnaire has been developed and validated and may become a useful adjunctive tool in the evaluation of RBD [26]. Overnight polysomnography with video recording should be performed in order to confirm the relationship between REM sleep and the complex motor behaviors. Clinicians should pay close attention to the presence of intermittent elevations in muscle tone or limb movements on the electromyelogram channel during REM sleep, a finding that is highly suggestive of RBD.

Circadian rhythm sleep disorders

Circadian rhythms are 24-hour biological rhythms, such as core body temperature and the sleep–wake cycle, controlled by an internal pacemaker located in the suprachiasmatic nucleus of the anterior hypothalamus. These rhythms are synchronized to the 24-hour day by external zeitgebers (i.e. time-givers or cues) such as light and activity and by internal rhythms such as body temperature and melatonin secretion. If one of the various contributors to the circadian rhythm becomes uncoupled or desynchronized from the others, then circadian rhythm sleep disorders (CRSDs) may develop.

In the elderly, a number of factors associated with aging likely contribute to the desynchronization of rhythms. The circadian pacemaker itself may degenerate with age, resulting in less robust rhythms, and there is a gradual decrease in the amplitude of the rhythm which may lead to less consistent periods of sleep–wake across the 24-hour day [27]. The endogenous secretion of melatonin at night is reduced with age, which may result in a weaker circadian rhythm. In addition, older adults may no longer have the same response to external zeitgebers and/or are exposed to fewer of them, such as the light–dark cycle. Studies have found that, in general, older adults spend little time exposed to bright light, averaging from about 30 minutes of bright exposure for Alzheimer's disease patients living at home to zero minutes for nursing home patients [28, 29, 30]. This low level of light exposure is associated with sleep fragmentation and desynchronized rhythms in institutionalized older adults [30].

The most common circadian shift seen in the elderly is advanced sleep phase (ASP), which is characterized by a shift or advance in the sleep–wake cycle and is manifested as habitual (and involuntary) sleep and wake times that are several hours earlier than societal norms. Patients with ASP feel sleepy in the early evening, timed with the drop in body temperature, and awaken in the very early morning. Sleep itself is normal, but delays in sleep onset related to obligations or societal behavior often result in an insufficient amount of sleep, as they awaken in the early morning regardless of what time they went to sleep, and excessive sleepiness during the day. If patients ignore their rhythm (i.e. sleepiness) in the early evening or inadvertently fall asleep watching television, when they actually get into bed, they may experience great difficulty falling asleep and subsequently complain of sleep onset-insomnia, typically coupled with an early morning awakening.

ASP is thought to be related to a combination of factors including decreased light exposure, which subsequently causes changes in the core body temperature cycle. There may also be a genetic predisposition [31]. The prevalence of ASP is approximately 1% in younger adults and although the prevalence appears to increase with age, the exact rate has not yet been established in older adults. Patients may learn to function with the advance in their sleep–wake cycle and therefore not present to their clinician for evaluation. Those elderly patients who do present to their clinicians may report trouble falling asleep or early morning awakenings, similar to patients with sleep-onset insomnia or depression.

In order to recognize advanced sleep phase, a careful and detailed sleep history along with a 1–2-week patient-completed sleep diary should be obtained. Activity monitoring with wrist actigraphy, which records the patient's underlying circadian rhythm and allows for an objective examination of the patient's sleep–wake cycle, can also be useful in making the diagnosis.

Insomnia

Insomnia is defined as difficulty initiating or maintaining sleep or non-restorative sleep, which results in daytime consequences and dysfunction [32]. Many elderly patients will report that they are unable to stay asleep throughout the night and/or wake up in the early morning and are unable to fall back to sleep.

In the older adult, it is important to recognize that subjective complaints of insomnia are often co-morbid with medical and/or psychiatric conditions, medication use, and behavioral and/or psychosocial factors. In a study of insomnia in older adults, 28% of subjects complained of chronic insomnia, but only 7% of the

new cases occurred in the absence of one of these related conditions [33]. Complaints of sleep difficulties in the elderly are strongly associated with complaints about health and depression [34]. In the 2003 National Sleep Foundation survey of adults aged 65 years and over, the respondents with more medical conditions, including cardiovascular, pulmonary, neurological and psychiatric diseases, reported significantly more sleep complaints, and the likelihood of having sleep complaints increased as the number of co-morbid medical conditions present increased [35]. In a different study that examined the impact of medical co-morbidities on sleep problems, insomnia was associated with a variety of medical conditions including cardiovascular disease and arthritis [36]. A study that included more than 3000 adults reported that between 30–50% of patients with myocardial infarction, angina, congestive heart failure, hip replacement, diabetes mellitus, or prostate disease complained of insomnia [37]. Patients with chronic medical disease appear particularly prone to sleep disturbances with studies finding that 31% of patients with arthritis and 66% of patients with chronic pain report difficulty with falling asleep, 81% of patients with arthritis, 85% of patients with chronic pain, and 33% of patients with diabetes mellitus report trouble with staying asleep, and 45% of patients with gastroesophageal reflux disease, 50% of patients with congestive heart failure, and 44% of patients with cancer report difficulty with both falling and staying asleep [38, 39, 40, 41, 42, 43]. Shortness of breath (due to chronic obstructive pulmonary disease or congestive heart failure), nocturia (due to benign prostatic hypertrophy or diabetes mellitus), and neurological deficits (related to residual stroke deficits or Parkinson's disease) are all associated with complaints of insomnia [36, 44, 45]. The relationship between medical conditions and sleep difficulties has been confirmed in older adults as well. A study that included almost 5000 elderly patients who were followed for up to 4 years found that the incidence of sleep disturbances was associated with the presence of health conditions. The persistence of the sleep disturbance, however, was best predicted by the presence of depression at follow-up [44].

Sleep difficulties are also associated with a number of psychiatric disorders with depression being strongly linked to insomnia [46]. In a telephone survey that included more than 24 000 adults of all ages, insomnia was present in 65% of respondents with major depression, 61% of those with panic disorder, and 44% with generalized anxiety disorder [47]. While the anxiety, stress, and/or depression related to stressful life events such as the death of a spouse or friend can lead to a bout of transient insomnia, in some cases, these events can trigger long-lasting, chronic insomnia. In addition, patients with insomnia are more likely to have a psychiatric disorder [48], and having insomnia at baseline is a significant predictor of developing depression 1–3 years later [49, 50]. Older women with insomnia seem to be especially susceptible to depression [48, 51, 52]. Treatment of insomnia has been reported to improve depression in younger adults [53], but such studies have not yet been conducted in older adults.

The medications used to treat medical and psychiatric disorders can also significantly contribute to or even cause sleep disruptions. If taken late in the day, a variety of medications may cause difficulty falling asleep at night. Medications such as central nervous system stimulants (e.g. dextroamphetamine, methylphenidate), antihypertensives (beta-blockers, alpha-blockers, calcium channel blockers), bronchodilators (theophylline, albuterol), corticosteroids, decongestants (pseudoephedrine, phenylephrine), diuretics, and antidepressants (protryptyline, buproprion, selective serotonin re-uptake inhibitors, venlafaxine, monoamine oxidase inhibitors) are all known to cause insomnia as an adverse effect. In contrast to these stimulating medications, older adults often also take a variety of medications that can cause sedation and daytime sleepiness, which may lead to unintentional napping if taken early in the day. Medications such as sedatives-hypnotics, antihistamines, antidepressants (amitriptyline, doxepin, trimiprimine, trazodone, mirtazepine), and dopamine agonists can all contribute to excessive daytime sleepiness, which could potentially contribute to sleep onset insomnia or exacerbate/maintain existing insomnia. To avoid the potential adverse effects on sleep, clinicians should advise patients to take sedating medications prior to bedtime and stimulating medications and diuretics in the morning.

Given the number of factors that can contribute to or cause insomnia, it is not surprising that the prevalence of insomnia in older adults is relatively high. In a study of more than 9000 older adults (≥65 years of age), 42% reported difficulty both falling and staying asleep and 28% reported trouble with falling asleep [34]. While the sleep complaints had resolved in 15% of the study's population 3 years later, the incidence of new sleep complaints was 5% [33]. The prevalence of

chronic insomnia appears to increase with increasing age as a telephone survey of 1000 randomly selected adults found that the prevalence of chronic insomnia was highest in those aged 65 years and over [54]. This same study also found that the prevalence of occasional or transient insomnia did not change with age [54]. A different study that included more than 13 000 participants aged 45 to 69 years reported that when medical/psychiatric illnesses, medications, and other confounders that are believed to contribute or cause trouble with sleep were controlled for, the prevalence of insomnia did not increase with increasing age [55]. This study's findings underscore the significant impact that these factors can have on sleep. Most epidemiological studies have found that the prevalence of insomnia in older women is higher than that in older men [56].

As discussed in previous sections, insufficient sleep, whatever the cause, can have significant consequences. Insomnia has been reported to contribute to reduced quality of life and changes in mood, and specifically increased symptoms of depression and anxiety [57]. Insomnia is also associated with mental and physical performance deficits, including slower reaction time, imbalance, and trouble with memory and concentration [58]. Older adults with insomnia may suffer from diminished cognitive function that may be mistaken for dementia [59], and one study reported that insomnia was a stronger predictor for placement of its elderly subjects in nursing homes than was the diagnosis of dementia [60]. The presence of long-standing chronic insomnia is associated with overall poor health status and a number of chronic medical conditions [33, 34].

Summary

Despite the increased prevalence of certain sleep disorders and known changes that occur in both sleep architecture and circadian rhythms in the elderly, poor and/or disrupted sleep is not an inevitable part of growing older. Complaints about sleep in older adults may be due to specific sleep disorders, changes in circadian rhythms, medication use, or co-morbid medical and/or psychiatric conditions. Clinicians who care for elderly patients should be educated about the normal and the pathological changes in sleep found in this population. As with younger patients, sleep complaints in older patients should be evaluated with a thorough sleep history and often an overnight sleep study. The appropriate diagnosis or identification of specific, often reversible or correctable factors contributing to an elderly patient's sleep complaint can result in significant improvements in quality of life and daytime functioning.

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Part 3
Chapter
12

Sleep disorders in the elderly

Circadian rhythm dysregulation in the elderly: advanced sleep phase syndrome

David K. Welsh and Louis J. Ptácek

Introduction

Symptoms of abnormally early sleep are common in the elderly. Aging is associated with earlier habitual bedtimes and earlier morning wake-up times [1, 2]. Older subjects also tend to score higher on "morningness," a subjective measure of preference for earlier sleep timing, based on the Horne-Ostberg Morningness-Eveningness Questionnaire (MEQ) [3]. In a large multicenter study of 9000 subjects aged 65 years or older, about 20% complained of early morning awakening [4]. If the symptoms are not attributable to other disorders, elderly patients with chronic or recurrent complaints related to early sleep timing may be diagnosed with the circadian rhythm sleep disorder commonly known as advanced sleep phase syndrome.

Circadian rhythm sleep disorders

Circadian rhythm sleep disorders are disruptions of sleep timing caused by either abnormal circadian clock function or misalignment between the clock and external schedules [5, 6]. Jet lag and shift work are "extrinsic" disorders, in which the problem is a mismatch between the normal sleep–wake rhythm and an altered external schedule imposed by transmeridian flight or work demands (see Chapter 13). Intrinsic disorders, on the other hand, are those in which the endogenous circadian regulation of sleep is itself abnormal. These intrinsic disorders include irregular sleep–wake rhythm, free-running disorder, and delayed sleep phase syndrome (DSPS), as well as advanced sleep phase syndrome (ASPS). The American Academy of Sleep Medicine has published official descriptions and diagnostic criteria for these disorders in *The International Classification of Sleep Disorders*, 2nd edition (ICSD-2) [7].

Irregular sleep–wake rhythm

In this disorder, sleep is highly fragmented throughout the 24-hour day, and there is no clear circadian organization at all. This disorder occurs almost exclusively in patients with neurological disorders, including elderly patients with dementia, and is thought to result from damage to the central circadian clock or its output pathways. However, partial loss of circadian organization can be induced even in normal subjects confined to bedrest with minimal cognitive stimulation [8]. This is because normal circadian sleep–wake organization is mediated partly by circadian timing of waking behaviors that are incompatible with sleep, and limiting these behaviors (as is common in nursing home environments, for example) can result in substantial sleep–wake fragmentation [9].

Free-running disorder

In free-running disorder (also known as "non-24-hour sleep–wake disorder"), circadian organization is intact, but the sleep–wake rhythm is not synchronized to the 24-hour day, and "free-runs" with its own endogenous circadian period, usually longer than 24 hours. Thus, patients complain of insomnia and daytime somnolence that wax and wane every few weeks, as their internal clock drifts in and out of phase with the environment. This disorder is relatively common in the blind, but rare in sighted individuals; it is thought to be due to decreased sensitivity or exposure to the synchronizing effects of light.

Delayed sleep phase syndrome

In delayed sleep phase syndrome (DSPS), the sleep–wake rhythm is still synchronized to the 24-hour day, but at an abnormally late phase: patients prefer to fall asleep and wake up several hours later than dictated by work or social demands. A key feature of this disorder is that sleep is normal when it is allowed to occur at the preferred later clock time. However, problems arise when patients try to conform to a conventional schedule, leading to complaints of evening insomnia, difficulty awakening on time in the morning even with an alarm, and morning somnolence. These complaints

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often persist even when a conventional sleep–wake schedule is imposed, with enforced bedtimes and wake-up times. Delayed sleep phase syndrome is thought to be due to increased sensitivity or exposure to evening light (which delays rhythms), decreased sensitivity or exposure to morning light (which would ordinarily advance rhythms earlier), or a long intrinsic period of the circadian clock. Another possible cause of delayed sleep phase is altered coupling between the central circadian clock and other brain centers controlling sleep. DSPS may occur in the elderly, but it is much more common in teenagers and young adults. On the other hand, ASPS, which is in many ways the opposite of DSPS, is more common in the elderly than in younger individuals.

Diagnosis of ASPS

In advanced sleep phase syndrome (ASPS), sleep timing is abnormally early compared to a conventional or desired schedule. In the official ICSD-2 description and diagnostic criteria (Table 12.1), it is now referred to as "Circadian Rhythm Sleep Disorder, Advanced Sleep Phase Type", or "Advanced Sleep Phase Disorder" [7]. Patients with this disorder typically complain of early evening sleepiness, early sleep onset (18:00–21:00), and spontaneous early morning awakening (02:00–05:00). If patients resist evening sleepiness and delay sleep to a conventional bedtime, they still wake up early, leading to daytime sleepiness. Daytime or early evening naps may then lead to difficulty falling asleep at the conventional bedtime, thus complicating the diagnosis. However, ASPS can often be recognized by a clear preference for an earlier sleep schedule when "on vacation," in the absence of work or social demands, and by the fact that sleep at the preferred earlier time is normal.

Sleep log or objective monitoring by actigraphy should establish "a stable advance in the timing of the habitual sleep period" for at least a week, preferably two weeks or longer. Routine polysomnography (PSG) is not indicated for this disorder, but may be necessary to rule out suspected sleep apnea, periodic leg movements, or another sleep disorder. If PSG is performed, it should be scheduled at the patient's preferred (early) sleep time. PSG studies of patients with ASPS show essentially normal sleep when PSG is performed at the early sleep time, but if performed at the conventional time may show reduced sleep latency and REM latency, reduced sleep time, and early morning awakening. Phases of core body temperature and melatonin rhythms are generally advanced, though typically less so than sleep timing. ASPS patients generally score as definite "morning types" on the Morningness–Eveningness Questionnaire (MEQ) [3].

Table 12.1. Diagnostic criteria for advanced sleep phase syndrome (ASPS), also known as advanced sleep phase disorder

	Circadian Rhythm Sleep Disorder, Advanced Sleep Phase Type (Advanced Sleep Phase Disorder) 327.32
A	There is an advance in the phase of the major sleep period in relation to the desired sleep time and wake-up time, as evidenced by a chronic or recurrent complaint of inability to stay awake until the desired conventional clock time, together with an inability to remain asleep until the desired and socially acceptable time for awakening
B	When patients are allowed to choose their preferred schedule, sleep quality and duration are normal for age with an advanced, but stable, phase of entrainment to the 24-hour sleep–wake pattern
C	Sleep logs or actigraphy monitoring (including sleep diaries) for at least 7 days demonstrate a stable advance in the timing of the habitual sleep period*
D	The disturbance is not better explained by another sleep disorder, medical or neurological disorder, mental disorder, medication use, or substance use disorder

**Note*: In addition, an advance in the timing of other circadian rhythms such as the nadir of the core body temperature rhythm or dim light melatonin onset (DLMO), is useful for confirmation of the advanced circadian phase.

Official diagnostic criteria specified by the American Academy of Sleep Medicine, revised in 2005, as published in *The International Classification of Sleep Disorders,* 2nd ed. (ICSD-2) [7].

For all circadian rhythm sleep disorders, ICSD-2 diagnostic criteria require that insomnia and/or daytime sleepiness cause functional impairment. Finally, the diagnosis requires that the symptoms are not "better explained" by another sleep disorder, or by a medical, neurological, psychiatric, or substance use disorder. Among psychiatric disorders, it is particularly important to rule out major depression, bipolar disorder, or general anxiety disorder, which commonly cause early morning awakening [10] (see Chapter 11).

Prevalence of ASPS

Advanced sleep phase syndrome has been thought to be quite uncommon, at least when strictly defined. It was initially documented in a few case reports [11, 12]. Not a single case was found in a survey of 10 000 Norwegian adults (ages 18–67) [13]. Among patients

seeking medical attention for sleep problems who were diagnosed with a circadian rhythm sleep disorder (N=322), only 1.2% were classified as having ASPS [14].

However, in reality, advanced sleep phase is much more common than these figures would suggest, because most patients do not complain of symptoms or come to medical attention. Whereas delayed sleep phase prevents people from getting to school or work on time, advanced sleep phase is more compatible with societal demands. With proper scheduling, people with advanced sleep phase can usually manage to meet their school, work, and social obligations; thus, lacking substantial impairment, they may not seek help or meet strict ICSD criteria for ASPS. Many cases come to medical attention only because of marital conflict, when the patient's spouse complains about the patient falling asleep too early. The elderly are even less likely to complain than younger people with advanced sleep phase, because they may not have rigid school, work, or social schedules.

Thus, despite the low reported prevalence of strictly defined ASPS, advanced sleep phase is probably rather common in the elderly. As mentioned previously, aging is clearly associated with earlier sleep timing and morning preference [1, 2], and in one survey study of adults 65 or older, about 20% complained of waking up too early in the morning [4]. Further studies are needed to establish the true prevalence of ASPS in the elderly.

Pathophysiology of ASPS

Circadian pacemaker

Sleep and many other physiological and behavioral processes occur in daily rhythms orchestrated by a circadian (*c.* 24-hour) pacemaker in the hypothalamus [15] (see Chapter 1). Neurons of this central pacemaker, known as the suprachiasmatic nucleus (SCN), are normally synchronized to the 24-hour light/dark cycle by photic input from the retina, and are also influenced by the hormone melatonin. SCN neurons then, in turn, synchronize subsidiary circadian oscillators in cells throughout the body, through autonomic, humoral, and behavioral output [16]. Even without light input, SCN cells remain rhythmic, remain synchronized to one another, and maintain the synchrony of peripheral oscillators, but the system adopts a "free-running" circadian period slightly different from 24 hours. Under such conditions, human subjects exhibit prominent circadian rhythms of sleep–wake, core body temperature, and hormone secretion, with an intrinsic period of ~24.2 hours [17]. Under normal day/night conditions, on the other hand, integrated effects of morning light (which shifts the SCN clock earlier) and evening light (which delays it) ordinarily synchronize (or "entrain") all these rhythms to the exactly 24.0 hour day–night cycle. An important consequence of this entrainment mechanism is that subjects with shorter intrinsic periods, greater sensitivity to morning light, or reduced sensitivity to evening light, will tend to entrain at earlier phases in a day–night cycle [18].

Intracellular circadian clocks

At a cellular level, circadian rhythms are thought to be driven by a delayed transcriptional negative feedback loop [15]. In this loop, CLOCK-BMAL1 heterodimers activate transcription of a set of *Period* and *Cryptochrome* genes (*Per1, Per2, Per3, Cry1, Cry2*). After delays associated with the transcription, translation, phosphorylation, and nuclear translocation of PER and CRY proteins, they form heterodimers, which inhibit transcription of their own genes. Regulated degradation of PERs and CRYs then relieves the inhibition, allowing the cycle to begin anew [19].

Sleep timing

Human sleep is not timed exclusively by the circadian system, but rather by a complex interplay among environmental factors (e.g. light, noise, meal schedules, social demands), behavioral selection of bedtimes and wake-up times, the circadian pacemaker (in the SCN), and a homeostatic mechanism (poorly defined anatomically) that preserves a balance between sleep and wakefulness [20] (see Chapter 10). Pressure for sleep builds up exponentially with time awake, and dissipates with time spent asleep. Long episodes of uninterrupted daytime wakefulness and nocturnal sleep occur in humans because circadian alerting signals increase over the course of the day, counteracting the accumulating homeostatic sleep pressure, then fall throughout the night as homeostatic sleep pressure declines. Environmental, behavioral, or homeostatic factors can also interact in complex ways with the circadian system by influencing light exposure.

Possible etiologies

Theoretically, then, ASPS could result from a variety of abnormalities in sleep regulation. If there is an

abnormally early circadian rhythm of sleep propensity, this could be due to altered coupling between the SCN clock and other neural centers controlling sleep, increased SCN sensitivity or exposure to morning light, decreased SCN sensitivity or exposure to evening light, or a short intrinsic circadian period. Familial forms of ASPS have been identified in which early sleep phase is, in fact, due to a short intrinsic period of the circadian clock, determined at the molecular level by a single DNA base change in a clock gene [21] (see below). The early sleep timing associated with aging, however, is not due to a shorter circadian period, but rather to decreased circadian and homeostatic sleep drive late in the night, causing older people to wake up even earlier than their circadian clocks would otherwise dictate [22]. The increased early morning light exposure then compounds the problem by shifting the circadian clock earlier. Reduced sensitivity or exposure to evening light may also be involved. Thus, in some cases ASPS is due to a defective circadian clock; in other cases, behavioral or homeostatic factors can shift the clock earlier by altering light exposure through early self-selected bedtimes or abnormally curtailed sleep.

Studying human circadian rhythms

Measuring sleep

A common subjective estimate of preference for early versus late sleep phase is given by the "morningness" preference score on the Horne-Ostberg Morningness-Eveningness Questionnaire (MEQ) [3], or the more comprehensive Munich Chronotype Questionnaire [23]. Actual sleep times can be estimated by sleep diary, wrist actigraphy, or polysomnography.

Measuring phase

Phase of the human SCN circadian pacemaker must be measured indirectly. The fitted minimum of the core body temperature rhythm (*T*min) is often used as a marker of endogenous circadian phase [17]. Another good phase marker is dim-light melatonin onset (DLMO), the time of nocturnal increase in melatonin production as detected in blood or saliva, in the absence of suppression by bright light [24, 25]. *T*min and DLMO are more direct and reliable estimates of SCN clock phase than sleep times, which are subject to regulation by various non-circadian processes, as noted above.

In estimating endogenous circadian phase or amplitude from physiological rhythms, it is important to control for acute "masking effects" of such confounding variables as behavioral activity, sleep, posture, meals, or light [22, 26]. Investigators may attempt to remove masking effects by simply subtracting them from rhythm data. However, it is difficult to estimate masking accurately, because it may vary among individuals and across circadian phase. A better solution is to use experimental strategies that distribute the masking influences uniformly across circadian phase. In the constant routine protocol, subjects are kept awake in bed in a fixed posture, with constant dim light and hourly liquid meals. In young adults, the phase of core body temperature minimum (*T*min) occurs at ~06:00 [2].

Measuring period

In estimating intrinsic circadian period under free-running conditions, it is important to control for effects of light. In conventional free-running studies in which patients have control of their own lighting, preferential selection of phase-delaying evening light tends to artificially lengthen period to ~25 hours [22, 27]. One solution is to minimize light input to the circadian pacemaker at all times, either by using very dim lighting (e.g. 8 lux) or by using blind subjects. Alternatively, in the forced desynchrony protocol, subjects are placed on a light–dark cycle too long or too short to synchronize them; thus, they free-run through all possible phase relationships with the light–dark cycle. With proper controls for light exposure, intrinsic circadian period in humans is ~24.2 hours [17].

Familial ASPS (FASPS)

Early hints

Even before the identification of familial ASPS (FASPS), there were indications from animal and human studies that ASPS could have a substantial genetic component. *Tau* mutant hamsters have an abnormally short free-running period of the locomotor activity rhythm (~20 hours for homozygotes), and early timing of locomotor activity in a 24-hour light–dark cycle [28]. *Tau* is an autosomal, semidominant mutation of the *casein kinase I epsilon* (*CKIε*) gene [29]. By enhancing the function of the kinase *in vivo*, the *tau* mutation accelerates degradation of PER proteins, thereby speeding up the clock [30, 31]. In humans, hints of a genetic basis for ASPS came from twin studies indicating nearly 50% heritability of

"morningness" preference (MEQ) [32, 33]. In addition, a number of studies, recently reviewed by Ebisawa [34], have since identified statistical associations between various polymorphisms of clock genes (*Per* or *Clock*) and MEQ, ASPS, or DSPS.

Discovery of FASPS

In 1999, three US families of Northern European descent were identified in which ASPS occurred at high prevalence, in a pattern consistent with single gene autosomal dominant inheritance with high penetrance [35]. In affected individuals, there was a 3–4-hour phase advance of sleep (19:25–04:18), melatonin (DLMO 17:31), and core body temperature rhythms (*T*min 23:22), and a distinct morning preference (MEQ 76.2). By history, onset of the early sleep pattern was typically between 8 and 30 years of age. Polysomnography of sleep in six selected subjects (performed at preferred sleep times) revealed normal sleep structure and normal timing relative to temperature or melatonin rhythms. Interestingly, one of these six ASPS subjects met criteria for major depression, and two for "mild depression." One subject (from kindred 2174) studied in a standard free-run protocol had an abnormally short period of 23.3 hours (Fig. 12.1). Further work revealed that the phenotype in this kindred (but

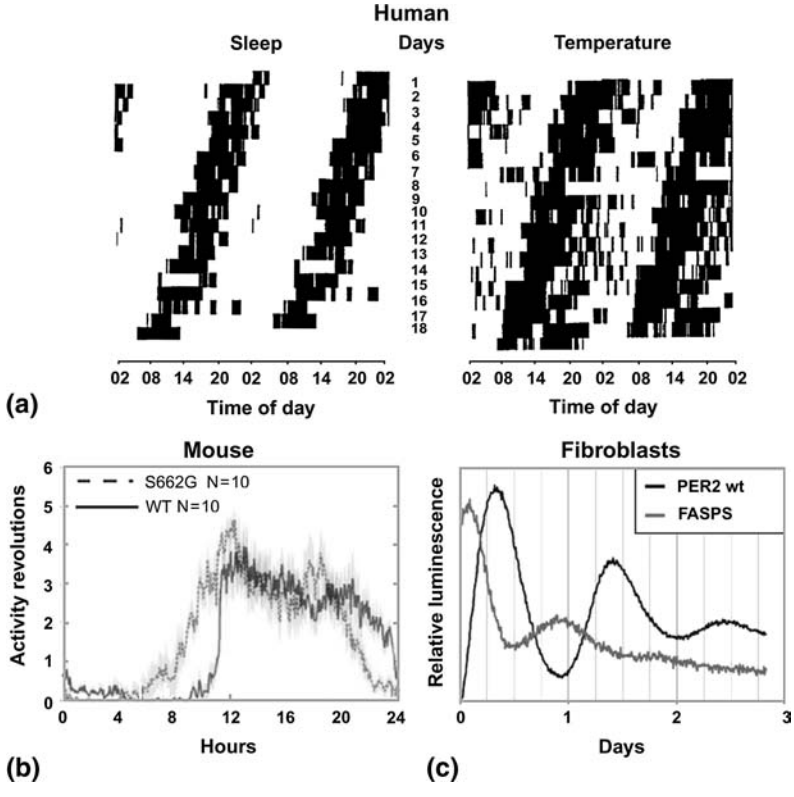

Figure 12.1. FASPS in humans, mice, and fibroblasts. A mutation in the circadian clock gene *Per2* is the cause of familial advanced sleep phase syndrome (FASPS) in a North American family [21, 35]. Affected individuals have abnormally early sleep timing under entrained conditions and a shortened free-running circadian period under constant conditions. (a) Free-running sleep and core body temperature rhythms of a FASPS subject from this family (kindred 2174) studied under constant conditions. Time of day is plotted left to right, each day is extended to 48 hours to enhance appreciation of patterns crossing midnight, 18 successive days are aligned vertically, and black bars represent polysomnographically recorded sleep (left) or temperature below the daily mean (right). Note that sleep occurs earlier each day, reflecting a 23.3-hour circadian period, in contrast to the ~25-hour periods of most normal subjects under these conditions. (From Jones *et al*. [35], reprinted by permission of Macmillan Publishers Ltd.) (b) Average locomotor activity rhythm of transgenic mice engineered to express the same mutation (PER2 S662G) and entrained to a 24-hour light–dark cycle, showing a phase advance compared to wild-type (WT) mice. In constant darkness, the mice exhibited an abnormally short free-running circadian period. (From Xu *et al*. [37], reprinted by permission of Elsevier.) (c) Circadian rhythm of clock gene expression in a population of fibroblast cells engineered to express the same mutant gene and previously entrained to a 24-hour temperature cycle, showing a phase advance compared to control cells. The cells also showed an abnormally short circadian period. Clock gene expression was measured using a firefly luciferase reporter driven by E-box regulatory elements from the *Per1* clock gene. (From Vanselow *et al*. [36], reprinted by permission of Cold Spring Harbor Laboratory Press.)

not in the other two) is caused by a single DNA base change in the *Per2* clock gene, leading to substitution of glycine for serine at position 662 of the PER2 protein (PER2 S662G) [21]. Thus, in this family, ASPS is caused by a point mutation in the clock gene *Per2*.

Cell and mouse models

The short period and advanced phase phenotypes of FASPS in kindred 2174 were subsequently reproduced in fibroblast and transgenic mouse models (Fig. 12.1). In NIH3T3 fibroblasts over-expressing the mouse version of the FASPS mutation, a luciferase reporter of clock gene rhythms revealed a short circadian period, and advanced phase when the cells were entrained by a 24-hour temperature cycle [36]. In transgenic mice expressing the human PER2 S662G mutation, locomotor activity rhythms revealed a short circadian period, and advanced phase in a 24-hour light–dark cycle [37]. Mechanistic studies indicate that the PER2 S662G mutation decreases phosphorylation of PER2, which reduces the overall rate of *Per2* transcription, allowing an earlier decline of PER2 and consequently a shorter circadian period.

Other forms of FASPS

Other FASPS families have been identified with similar autosomal dominant patterns of inheritance, but in which the mutation is not in the *Per2* gene [15, 21, 38, 39, 40] (Table 12.2). Phenotypes in these additional families were similar to those in kindred 2174, including 2–5-hour advances of sleep timing, and a high prevalence of depression in some cases. In one family [40], the responsible mutation causes a substitution of alanine for threonine at position 44 of the casein kinase I delta protein (CKIδ T44A). Transgenic mice expressing this mutation exhibit a shortened free-running circadian period. Interestingly, CKIδ is a very close relative of the CKIε protein mutated in the *tau* mutant hamster (see above), so the mechanism may be similar: accelerating PER degradation, thereby shortening circadian period [30].

ASPS of aging

ASPS is clearly more common in the geriatric population than in young adults, and the vast majority of geriatric ASPS cases are not familial. Rather, aging itself seems to affect the regulation of sleep timing, such that older people have earlier bedtimes, earlier wake times, and higher MEQ scores [1, 2]. Aging, in fact, has major effects on many aspects of sleep and circadian rhythms [22, 41, 42] (see Chapter 1).

Period

One possible explanation for ASPS of aging is that the intrinsic circadian period shortens with age, as it does with FASPS mutations. Early animal studies supported this idea, indicating that older rodents have shorter circadian periods of locomotor activity rhythms [43, 44]. However, more recent animal studies have been inconsistent [45, 46]. Moreover, human studies are now available, and show that there is no shortening of period with age. In a carefully designed forced desynchrony study comparing 64- to 74-year-old subjects with 21- to 30-year-old young adults, mean circadian period was 24.18 hours in both groups [17]. In a longitudinal study of blind subjects, period was slightly longer at a 10-year follow-up (averaging 48 vs. 38 years old) [47]. Also, circadian phase and sleep timing are not associated with circadian period in elderly subjects [48]. Thus, it appears unlikely that a shortening of circadian period with age is responsible for the increased prevalence of ASPS in the elderly.

Table 12.2. Familial advanced phase sleep syndrome (FASPS) pedigrees consistent with single gene autosomal dominant inheritance

References	MEQ	Sleep time	*T*min	DLMO	Mutation
Jones *et al.* [35], Toh *et al.* [21]	76.2	19:25–04:18	23:22	17:31	PER2 S662G
Reid *et al.* [38]	72.5	21:21–05:07		18:30	Unknown
Satoh *et al.* [39]	77.3	20:45–04:55		20:15	Unknown
Xu *et al.* [40]		18:12–04:06			CKIδ T44A

Shown for each pedigree are morning preference score from the Morningness-Eveningness Questionnaire (MEQ), average time of fitted minimum of the core body temperature rhythm (*T*min), average time of the dim light melatonin onset (DLMO), and the responsible circadian clock gene mutation.

Phase

It is clear that circadian rhythms of older subjects do entrain at an earlier clock time than in young adults. Cortisol, TSH, melatonin, and core body temperature rhythms are all advanced in the elderly [2, 49, 50]. However, elderly morning types not only wake up earlier relative to clock time, but also wake up at an earlier circadian phase (estimated by *T*min) [51], in contrast to younger morning types [51]. Elderly subjects in general also awaken at an earlier circadian phase than younger subjects [2, 52] (Fig. 12.2). In other words, sleep timing is even more advanced than other circadian rhythms in the elderly, which would not be true if an altered circadian clock were the sole underlying cause [20].

Amplitude

There are substantial age-related changes in sleep quality, above and beyond those explained by earlier circadian timing. In addition to a >1 hour phase advance of sleep, there is a 20–30% decrease in amplitude of the sleep–wake rhythm, due to increased awakenings from nocturnal sleep [22, 53, 54]. In some environments (e.g. nursing homes [9]), decreased daytime activity may lead to daytime napping and further reductions in amplitude [8]. However, reduced sleep–wake amplitude in the elderly is primarily due to decreased circadian drive to initiate sleep in the early morning and decreased homeostatic sleep drive at most phases [55]. Dissipation of homeostatic sleep pressure during sleep may also be more rapid in the elderly. Thus, age-related changes in both circadian and homeostatic sleep regulation contribute to early morning awakenings in older subjects, and the resulting exposure to morning light then advances the clock.

It is not clear whether this amplitude reduction is due to decreased need for sleep or a defect in the ability to maintain sleep. However, amplitudes of other circadian rhythms, including core body temperature, are also reduced with age [22], and post-mortem brain studies have revealed reductions in SCN volume, cell number, and neuropeptide rhythms [56, 57], suggesting an age-related clock defect. Amplitude reductions seen in animal studies also support this idea [41].

Light exposure

Behavior and lifestyle changes with age can also influence exposure to light, as demonstrated in naturalistic studies. Older subjects tend to be exposed to less bright light [58], particularly less evening light [59], often at very dim intensities [60]. Evening napping and darkness is associated with earlier wake-up times in elderly subjects [61] and advanced melatonin rhythms in young adults [62]. There is also increased exposure to mid-morning light (08:00–11:00) in the elderly [59], as well as to early morning light as a result of early morning awakening. Thus, reduced exposure to phase-delaying effects of evening light, and increased exposure to phase-advancing effects of morning light, probably both contribute to advanced circadian phase in the elderly.

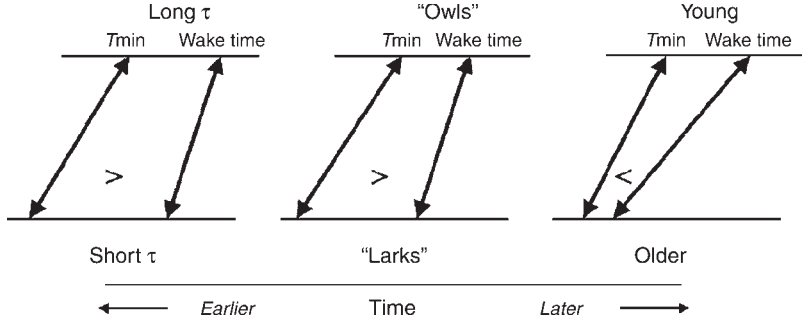

Figure 12.2. Schematic diagram illustrating phase relationships between circadian clock phase (*T*min) and wake-up time. The fitted minimum of the core body temperature rhythm (*T*min) is a reliable marker of circadian clock phase, whereas wake-up time also reflects other processes. Both are earlier relative to clock time in subjects with shorter periods, "Larks", and older subjects, but the phase relationship between them differs in these groups. Wake-up occurs later relative to *T*min (i.e. at a later clock phase) in human subjects with a short intrinsic circadian period (τ) relative to those with a long period, as well as in young "Larks" (morning types) relative to young "Owls" (evening types). In contrast, older subjects wake up *earlier* relative to *T*min (i.e. at an earlier clock phase) than do younger subjects. This indicates that the early sleep timing seen in ASPS of aging is not entirely due to an early circadian clock phase. (From Dijk and Lockley [20], reprinted by permission of the American Physiological Society.)

Light sensitivity

Another possible explanation for advanced circadian phase in the elderly is altered sensitivity to light. However, there is no evidence for an increase in sensitivity to the phase-advancing effects of morning light; in fact, one study found a decrease [63]. Several studies have found no change in sensitivity to phase-delaying effects of evening light in the elderly [63, 64, 65]. But these studies all used bright light (3000–10 000 lux), and even moderately bright room light can have significant phase-shifting effects in humans [66]. Recently, Duffy *et al.* [67] found that elderly subjects had smaller phase-delay responses to moderately bright evening light. Such reduced light sensitivity might be related to changes in lens opacity, pupil size, or retinal function, or to changes at the level of the SCN. In any event, reduction in sensitivity to the phase-delaying effects of moderately bright evening light may contribute to advanced circadian phase in the elderly.

Treatment of ASPS

Based on a systematic review of available literature [68], practice parameters for circadian rhythm sleep disorders were recently formulated by the American Academy of Sleep Medicine [69]. Treatments recommended for ASPS include chronotherapy, timed melatonin administration, and timed light exposure. These treatments are all directed towards the primary goal in treating ASPS: to correct the abnormally early timing of sleep by delaying the circadian clock. Of course, it is also important to treat co-morbid conditions that may contribute to sleep complaints, especially depression [10].

It is worth noting that ASPS is less likely than other sleep disorders to impair fulfilment of work or social demands, and may come to clinical attention only because of complaints of a spouse or other family member. If there is only mild distress or impairment, reassurance that a preferred early schedule is healthy may be all the treatment that is necessary.

Conventional options

Conventional options to treat insomnia (see Chapters 37–40) are generally not helpful for the early morning insomnia and evening sleepiness of ASPS, because they do not correct the underlying problem of phase misalignment. Sleep hygiene recommendations are generally not helpful, except that avoiding long evening naps may help to consolidate nocturnal sleep. Cognitive behavioral therapy (CBT) is not helpful. It may be tempting to use hypnotics for early morning awakening, but even short-acting benzodiazepine agonists are too long-acting to use in the early morning without risking daytime sedation and falls in the elderly; their use is not recommended for ASPS. Similar considerations apply to the use of modafinil (Provigil) to combat evening sleepiness; it is likely to interfere with nocturnal sleep, and is not recommended. However, any of these conventional options may have a role if ASPS is complicated by other forms of insomnia that do respond to improved sleep hygiene, CBT, or hypnotics.

Chronotherapy

The goal in treating ASPS is to correct the abnormally early phasing of sleep. Most ASPS patients find delaying their sleep schedule difficult, but advances much easier. Accordingly, advancing most of the way around the clock may be easier for some patients than delaying just a few hours. A prescribed schedule of 3-hour advances every 2 days for 2 weeks was successful in a single case report, with the new later schedule maintained even at a 5 month follow-up [12]. However, the transitional rotating schedule can be disruptive, and this strategy may not be practical for all patients.

Melatonin

Early morning administration of the hormone melatonin can induce phase delays in human subjects [70]. Melatonin has been used successfully to treat jet lag, shift work, DSPS, irregular sleep–wake rhythm, and free-running disorder [68]. Even though there is no evidence that it is effective for ASPS, there is a clear rationale for its use, and it is recommended by the American Academy of Sleep Medicine [69]. Optimal time of administration to produce phase delays is in the early morning hours [70], i.e. upon spontaneous early morning awakening in ASPS patients. It is important to minimize light exposure at this time, however, to avoid counteracting the delaying effects of melatonin with undesired advancing effects of early morning light. Effective doses range from 0.5 to 10 mg, but there may be an advantage in using the lowest doses, which allow more precise timing of physiological action [24]. A new alternative to melatonin is ramelteon (Rozerem), a melatonin agonist. Ramelteon has not been tested in ASPS either, but unlike melatonin its production is regulated by the US Food

Table 12.3. Light therapy for ASPS

	Light			Delays (hh:mm)			Sleep
References	lux	Hours	Days	*T*min	DLMO	Wake-up	Increased TST (min)
Lack and Wright [73]	2500	4	2	1:51	2:14	1:12	73
Campbell *et al*. [74]*	4000	2	12	3:08		0:18	46
Suhner *et al*. [72]*	4000	2	12	1:34		0:32	–
Palmer *et al*. [75]*	265	2–3	28		0:24	0:05	–
Pallesen *et al*. [76]*	10 000	0.5	21			0:21	20
Lack *et al*. [77]	2500	4	2	2:24	~2:00	0:57	92

Shown for each light therapy trial are light stimulus parameters, delays of circadian phase markers, and increases in total sleep time (TST). Light parameters: intensity in lux, duration in hours, and consecutive days of treatment. Circadian phase markers: fitted core body temperature minimum (*T*min), dim light melatonin onset (DLMO), and wake-up time. Some sleep data are from sleep diaries. Note that delay of wake-up and increase of TST were smaller in studies of mostly elderly subjects (*) than in the two studies by Lack [73, 77], which included a broader age range.

and Drug Administration (FDA), and it has a very favorable side effect profile (see Chapter 33].

Light

Light is the most potent phase-shifting stimulus in humans, and properly timed light exposure is the mainstay of treating ASPS. General recommendations are to minimize exposure to the phase-advancing effects of morning light and to maximize the phase-delaying effects of evening light [69]. Patients should stay indoors in a darkened room in the early morning, or wear sunglasses if they must go outdoors. They should stay outdoors in late afternoon and early evening sunlight, and then use bright indoor lighting in the evening. Bright lights for therapeutic use are commercially available. As the circadian photoreceptor is maximally sensitive at 480 nm [71], blue light may be more effective. Another consideration is that although older people can delay [63, 64, 65], they may require brighter light than young adults [67]. Finally, patient compliance with the bright light regimen should be verified [72].

Use of evening light in the treatment of ASPS is supported by a number of studies [72, 73, 74, 75, 76, 77], all of which included elderly subjects (Table 12.3). However, the most impressive results were obtained in the studies by Lack *et al*., which used subjects of a relatively broad age range (32–77 years old). They studied early morning insomniacs in a constant routine protocol, and found that 2500 lux for 4 hours (20:00–24:00) over 2 days delayed *T*min and DLMO by ~2 hours and wake-up time by more than 1 hour, and increased total sleep time (TST) by >1 hour [73]. A replication of this study produced similar results, with wake-up time delayed by nearly 1 hour and a 92-minute increase in TST [77].

The studies in older subjects produced more modest effects, although factors other than age may have been limiting in some cases. In the study by Palmer *et al*. [75], lower intensity lights were used, and the average DLMO phase delay was only 24 minutes. In the study by Pallesen *et al*. [76], it is not clear whether any phase delay was produced, because no reliable phase marker was measured. In the home studies by Campbell *et al*. [74] and Suhner *et al*. [72], compliance with the bright light regimen was not verified. Nevertheless, in these latter two studies of elderly subjects (ages 62–84), therapeutic effects on wake-up time and TST were relatively modest despite substantial phase delays of *T*min. Perhaps, as suggested by Suhner *et al*. [72], light is a less effective therapy for ASPS in the elderly than in younger subjects, due to a more complex etiology involving changes in homeostatic and circadian regulation of sleep (see section "ASPS of aging," above). In ASPS of aging, light would be expected to correct the underlying phase advance of the circadian clock, but would not be expected to alleviate early morning insomnia due to defects in circadian or homeostatic sleep drive.

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Part 3
Chapter
13

Sleep disorders in the elderly

Circadian rhythm dysregulation in the elderly: shift work

Timothy H. Monk

Introduction

Without doubt, *Homo sapiens* is a diurnal species. The most dominant of our five senses is that of vision, and for this and other reasons, we are built to be up and about during daylight and asleep at night. As noted elsewhere in this volume, there is an elaborate biological timekeeping system in the brain, the circadian system, whose function is to make the changes in human physiology necessary to accomplish that goal. Thus, working at night (or in the very late evening) is essentially an *unnatural* act. Because most definitions of shift work rest on patterns of work so defined, one can argue that shift work itself is unnatural. Of course, many of the things that humans do are unnatural, without necessarily being harmful. We wear clothes and live in heated homes, which are unnatural but beneficial. Other activities, though, such as smoking and driving fast cars, are often unnatural and harmful. Most current shift workers would argue that shift work fits into the latter category. There is evidence [1] that the circadian system changes with age, which suggests that shift work tolerance might also change. The purpose of this chapter is to discuss whether shift work might be particularly harmful to men and women over 55 years of age, who shall be referred to here as *seniors*.

What does shift work involve?

Different authors have different definitions of shift work. Here shift work will be defined as any regular paid employment outside the home that involves work after 21:00 on either a rotating or permanent basis, while excluding overtime requirements (even if such overtime is mandatory). Thus, this definition would, for example, include the convenience store clerk who works from 15:00 to 23:00 5 days per week, as well as the steelworker and nurse covering the midnight to 08:00 "graveyard" shift. It would not, though, include the accountant who works almost around the clock as tax time approaches. Because many seniors work part-time (e.g. to supplement retirement pension income), we shall include both part-time and full-time jobs.

Shift work, as defined above, has two key facets with regard to *work*, namely working past one's bedtime (evening shift), and working all night (night shift). As has been documented by several sleep diary and time budget studies [2], most night workers like to have their evenings free to be with family and friends and thus take their sleep immediately after work rather than after an interval of recreation. Also, late evening shift workers have few social activities or recreational possibilities open to them after work, and they too take their sleep as soon as possible after coming home from their job. Thus, the corresponding key attributes of shift work with regard to *sleep*, are those of delaying sleep onset by 2 or 3 hours (evening shift), or by 9 or 10 hours (night shift). The essence of the problem for seniors who are shift workers therefore revolves around three interrelated concepts: (1) age-related changes in the ability of the circadian system to phase adjust (i.e. to delay its timing); (2) age-related changes in the ability of the individual to stay awake and work in the late evening and overnight hours; and (3) age-related changes in the ability of the individual to sleep at "unusual" times (i.e. during the morning and early afternoon hours).

The picture is, however, a complicated one. As illustrated in Figure 13.1, the ability of an individual to cope with shift work rests upon an interactive quartet of factors. Thus, there are not only the sleep and circadian rhythm factors mentioned above, which interact with each other and are powerful determinants of coping ability; but there are also the social/domestic factors and the health factors. Similar to sleep and circadian rhythms, social/domestic and health factors also interact with each other, and also serve as a strong determinant of coping ability. For example, however well adjusted a senior's circadian rhythms might be to night duty, his/her day sleep may

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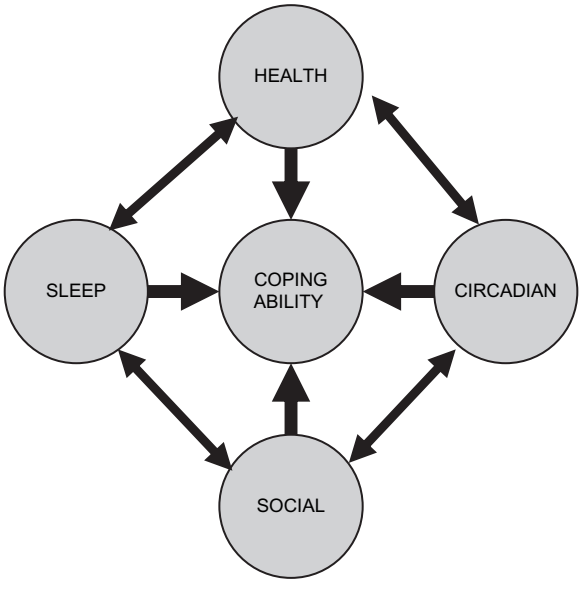

Figure 13.1. Conceptual model of the four interrelated factors governing an individual's ability to cope with shift work.

still be ruined by an uncooperative spouse, or by a sleep disorder perhaps resulting from a previous career as a shift worker. Thus, in addition to the three concepts mentioned above, one must add: (4) age-related changes in the individual's health; and (5) age-related changes in the individual's social/domestic milieu. These issues will be covered in turn in the chapter.

How many seniors are shift workers?

With the graying of the baby boom generation, the proportion of workers who are seniors is rapidly increasing. Thus, there is now a large cohort of individuals who are at or approaching retirement age, but either have insufficient money, or no desire, to retire from their jobs. In some cases in the USA, financial strain for the senior is exacerbated by companies reneging on their pension obligations. In many countries, legislation against "age discrimination" has removed rules regarding mandatory retirement, and has thus allowed seniors to make the decision to stay at their job beyond age 60 years or 65 years. However, especially in the manufacturing sector, the previous practice of allowing seniority within the company to enable older shift workers to bid their way out of shift work has largely disappeared. All too often nowadays, the decision is not one between *shift work* and *day work*, but between shift work and *no work*. In addition to demographic trends, there are also societal trends driving the issue. The fastest growing sector of most Western economies is the service sector, and increasingly, people are demanding and receiving around-the-clock availability of such services. Even in the production sector, plant machinery has become so expensive and so quickly obsolete that it has to be run 24 hours per day, 7 days per week, for it to be profitable. Very often employers specifically seek to hire seniors for such positions because of their greater experience and perceived reliability, relative to younger adults. Thus, shift work for seniors has become an issue of importance. Figures from the US Census Bureau (http://www.bls.gov/CPS) reveal that as of May 2004 there were more than 1.6 million seniors engaged in full-time shift work in the United States.

Circadian phase adjustment in seniors

Evidence can be gleaned from field studies in support of the assertion that seniors find circadian phase shifts difficult, and thus suffer more from jet lag and shift work. However, the data are largely from anecdotal observations and self-reports and have thus tended to concentrate more on sleep symptoms, rather than on more direct circadian measures such as rates of re-entrainment of circadian temperature or melatonin rhythms. As discussed in a later section, there is some evidence that late middle-aged shift workers experience more problems than young adult shift workers especially in regard to sleep (e.g. [3, 4]). A study by Harma *et al.* [5] is one of the few in which circadian rhythms were measured in seniors. Groups of young

(19–29 years) and late middle-aged (53–59 years) postal letter sorters were studied in their adjustment to three consecutive night shifts. Young subjects showed better phase adjustment (in circadian rectal temperature rhythm phase) than late middle-aged subjects to the required phase delay, as well as improved subjective sleep in the three consecutive day sleeps. Thus, even using a modest age differential, significant age effects in circadian phase adjustment rates emerged. There is rather little evidence in the jet lag situation since most field studies are concerned with young adults, but an early study by Preston [6] indicated that late middle-aged flight crew members had more problems than their younger colleagues. Later, Gander *et al.* [7] analyzed age effects in the large-scale NASA-Ames study of commercial aviation cockpit personnel, showing some detrimental effects of age in this fairly fit sample of pilots under 60 years of age.

In contrast, there is evidence from laboratory studies to *refute* the assertion that the rate of circadian phase shift slows with age. Monk *et al.* [8] performed a laboratory study involving a 6-hour phase advance in routine in older (71–86 years) and early middle-aged (37–52 years) subjects. The results indicated that whereas sleep was indeed more disrupted in the older subjects than in the early middle-aged, the effect could *not* be attributed to circadian temperature rhythm phase adjustment rates, which were almost identical between the two age groups. In a later publication, Monk *et al.* [9] compared phase delays with phase advances in older (67–87 years) subjects and showed that they exhibited a very similar directional asymmetry (phase advances were worse) to that conventionally seen in younger adults. In a more precise phase shift study involving the circadian response (in body temperature and plasma melatonin rhythms) to three consecutive 5-hour bright-light stimuli, Klerman *et al.* [10] also showed a remarkable similarity in phase-adjustment pattern between young adults and seniors, particularly in the phase-delay direction. Thus, laboratory evidence appears to suggest that the circadian systems of young and old may respond in a fairly similar way to abrupt phase shifts.

Sleep in seniors after circadian phase shifts

As noted above, there appears to be little doubt that the *sleep* of seniors is more disrupted than that of younger adults by phase shifts, even if that disruption cannot be directly attributable to age-related differences in circadian phase adjustment rates. Figure 13.2 illustrates the sleep disruption induced by the same circadian phase shift (a 6-hour phase advance) given to 6 young men, 8 middle-aged men, and 10 older men in an identical protocol. Plotted is the average sleep efficiency (percentage of the "night" actually asleep) for the 3 nights before and the 3 nights after the phase shift, excluding the night in which the shift actually occurred (data from [11, 12]). The main feature is the relative resilience in the sleep of the young men to the phase shift, in contrast to that of the middle-aged and older men; although, as expected, the older men started with a worse baseline (pre-shift) level of sleep efficiency.

Moving from the laboratory to field studies of actual shift workers, there is ample evidence of an age-related decline in the amount and quality of sleep obtained. However, the issue is not a simple one. It should be noted that even in those who have never worked shifts, sleep declines over the middle years of life [13]. In a nice illustration of this, Brugere and colleagues [4] report data from a large-scale French epidemiological study with 21 378 subjects, 9584 of whom were shift workers (according to a fairly broad definition of shift work). Sleep symptoms were extracted from the Nottingham Health Profile (NHP), a self-report questionnaire of health symptoms completed by all subjects on their annual visit to an occupational health specialist. Brugere and colleagues separated the subjects into those currently working

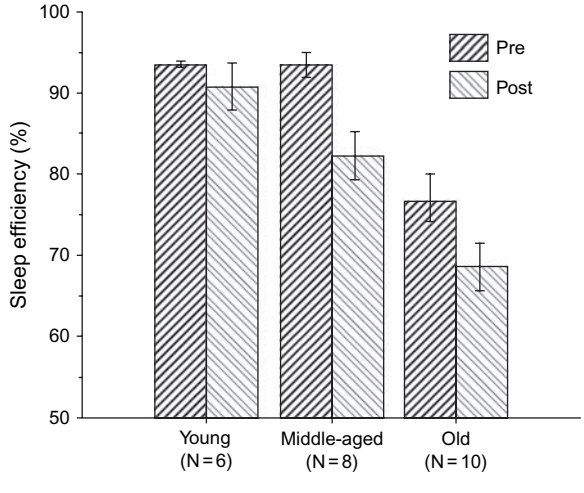

Figure 13.2. Mean sleep efficiency for the 3 nights before (pre) and 3 nights after (post) a 6-hour phase advance in 6 young men, 8 middle-aged men, and 10 older men in an identical protocol (data from [11] and [12]).

shifts ("present"), those who previously worked shifts but were not current shift workers ("past"), and those who had never been shift workers ("never"). Those with sleep disorders were defined as those answering in the positive to at least one of the five NHP questions concerned with sleep disorders. The frequency of sleep disorders (so defined) revealed the expected worsening with age. Interestingly though, the "past" line was intermediate between "never" and "present" lines, approaching the "present" line at the highest age group (52 years) – see Figure 13.3. Thus, although the two age-related curves (present and never) were largely parallel, the curve of the former shift workers (past) suggests some shift work is related to a build-up in sleep problems, even after shift work has ceased. Exposure to shift work in the past might thus be a risk factor for sleep disorders in retirement. This relates to the issues of health-related consequences of shift work discussed later in this chapter.

Also of relevance to the issue of shift working seniors' sleep is the age-related change that is observed in preferred circadian phase. From both anecdotal evidence and empirical study, it is clear that seniors have an earlier preferred bedtime and wake time, have more "morning lark" type scores on morningness questionnaires, and have earlier phasing marker rhythms of body temperature and melatonin production [1, 13] This change to an earlier preferred timing is important because, as noted above, evening shift workers get to bed late and have to sleep in late, and night shift workers usually commence sleep during the morning hours (typically at around 09:00). Thus, an earlier phasing circadian system and a more "morning-type" orientation would likely harm the shift worker's ability to have a successful morning sleep. This may itself render seniors more vulnerable to shift work sleep problems.

Night-time wakefulness in seniors

Conventional wisdom asserts that seniors have flatter (lower amplitude) circadian rhythms, rendering the difference between day and night in their physiology less different for them than it is for younger adults [14]. This view is supported by the increased daytime napping observed in seniors [15], and can also be invoked to explain some of seniors' inability to sleep well at night. Although a recent review [1] has cast doubt on the generality of an age-related reduction in circadian amplitude with regard to the key marker rhythms of body temperature and melatonin production, there does appear to be evidence that circadian rhythms in subjective sleepiness do indeed flatten with age [16]. Thus, although the senior's circadian pacemaker might be sufficiently strong to generate high-amplitude marker rhythms, such as core body temperature or plasma melatonin, the circadian signal no longer gets transduced into the rhythms governing sleep–wake behavior such as subjective sleepiness and sleep propensity, which then become relatively flat.

There are two sets of findings that support the assertion that the elderly may have lower amplitude sleepiness rhythms than younger adults, even when the reduction is not apparent in circadian temperature rhythms. The first comprises unmasking studies in which seniors were kept awake but in bed for 36 consecutive hours [16]. When hourly measures were compared, the results showed that for seniors there was a significant attenuation of rhythm amplitude in both sleepiness and performance measures (relative to young adult controls), even in seniors who were able to generate robust circadian temperature rhythms. The effect was particularly clear in older men for whom the effect of the circadian pacemaker on sleepiness and performance rhythms appeared to be largely absent. Thus, during the night hours, the older men

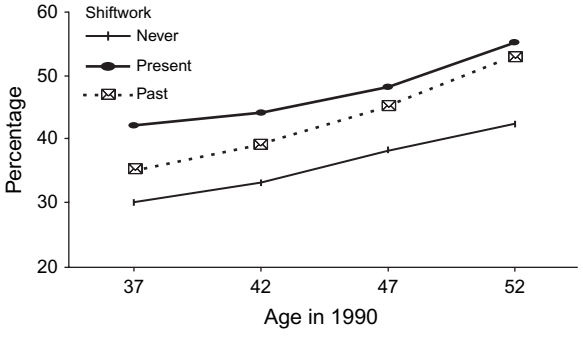

Figure 13.3. Percentage of subjects (total N = 21 378) reporting sleep disorders as a function of age, separately for those who had never worked shift work (Never), were presently shift workers (Present), or who had been shift workers in the past but were no longer shift workers (Past). (Reproduced from Brugere *et al.* [4] with permission.)

were not subject to an increase in sleepiness from the influence of the circadian pacemaker being at its low ebb at that time (typically around 04:00). This finding is also in accord with our own anecdotal observations in running the study, where in the middle of the night the seniors who were subjects appeared to find it easier to stay awake all night than did the young adult technicians paid to monitor them! The second set of findings come from "90-minute day" studies in which groups of young and older adult subjects were repeatedly allowed to sleep for 30 minutes and be awake for 60 minutes [17]. This allowed circadian rhythms to be plotted in sleepiness and sleep propensity, as well as in core body temperature. Although there was no age difference in body temperature rhythm amplitude, there was a significant age-related reduction in the amplitude of the circadian sleepiness and sleep propensity rhythms. This amplitude reduction led to seniors showing a relatively *lower* sleep propensity during the night hours. Thus, paradoxically, if one needs to stay awake all night at work, it may actually *help* to be a senior.

Age-related changes in mental and physical health

As noted above, a further determinant of a senior's ability to cope with shift work will be his or her state of health. There is little dispute that, on average, seniors have more health problems than younger adults. However, if a history of shift work leads to added health problems over and above those due to the normal aging effect, then (unless the senior is starting shift work de novo), there will be added reasons for him or her to have shift work coping problems stemming from poor health issues. There are several recent reviews that confirm that shift work can be hazardous to one's health [18, 19, 20]. An example of this in relation to sleep disorders has been mentioned earlier. It is possible that years of shift work experience renders the sleep and/or circadian system more vulnerable to sleep disorders [4]. Additionally, as discussed below, shift workers may have a tendency to become overweight, which would then increase the likelihood of sleep apnea syndrome.

A number of recent reviews have documented the health consequences of shift work [18, 19]. First, of course, are the obvious problems related to daytime sleep and sleepiness during the night shift, which can be very troubling to the individual concerned and in some cases (e.g. in the long-haul trucking industry) can compromise safety. Several international classifications also refer to a sleep disorder associated with abnormal work hours. The International Classification of Sleep Disorders [21] formally lists shift work sleep disorder as one of the circadian rhythm sleep disorders. The *Diagnostic and Statistical Manual of Mental Disorders* [22] lists shift work type as a subtype of the circadian rhythm sleep disorder (#307.45). Thus, there is increasing formal acceptance that the difficulties of sleep and wakefulness which some people experience with shift work should properly be regarded as a disorder worthy of medical diagnosis and treatment.

In addition to disorders of sleep and wakefulness, there appear to be both physical health and mental health consequences of shift work exposure. In terms of physical health, the main problems implicated are gastrointestinal disorders, cardiovascular disorders, and cancer. All are non-trivial, and cannot be put down simply to lifestyle factors attributed to shift work such as diet and smoking. For example, in one study, having more than 10 years of shift work exposure doubled the risk of cardiovascular disease [23]. Other more recent studies have confirmed the relation between shift work and cardiovascular disease, even when other risk factors are controlled for [19]. In a prospective study of almost 80 000 nurses, extensive (>30 years) rotating night work exposure increased the risk of breast cancer by 36% [24]. This increase has been confirmed in other studies [25], although there has been a recent very large-scale Swedish study [26] that found *no* effect of shift work exposure on the risk of *any* type of cancer. In terms of mental health, neuroticism, substance abuse, and alcohol abuse increases have all been implicated in rotating shift workers [27]. Also, in a preliminary study using a telephone psychiatric interview of 98 current and former shift workers, Scott *et al*. [28] have shown there to be a more than five-fold increase in the lifetime prevalence of formally diagnosed major depression in those with 6–20 years of shift work exposure as compared to those with less than 5 years of exposure. This latter finding is particularly important because of the evidence that depression per se may lead to sleep disorders and circadian dysfunction [29].

Clearly, any consideration of the health effects of chronic shift work must also be concerned with the *weight* (or rather the body mass index – BMI) of the worker. From research at the University of Chicago

(summarized in [30]) it is now well established that partial sleep deprivation affects glucose tolerance, and it would thus not be surprising were such effects not compounded with the poor dietary choices that shift workers often make (or are forced to make), to result in increased BMI, and an increased likelihood of sleep apnea and type 2 diabetes, as years of shift work exposure increase. Supportive evidence for this comes from a study from the Netherlands which concludes that BMI increases with shift work experience [31], a study from Sweden which concludes that there is an association between shift work and the metabolic syndrome [32], and a study from Japan that shift work is associated with insulin resistance in shift workers younger than 50 years [33].

The above evidence suggests that there may be additional burdens placed on the older shift worker because of his or her health issues, especially if shift work in the senior years follows on from shift work exposure in the young adult and middle-aged years. Such burdens may take the form of illness-related discomfort further disrupting sleep, the need to take medications which may themselves disrupt sleep, the sleep disorders of insomnia and sleep apnea, as well as psychiatric disorders such as depression.

Age-related changes in the social/domestic milieu

Although scientists and clinicians have quite naturally tended to concentrate on the physiological and health problems associated with shift work, there are also important social and domestic issues to be considered. Human beings are essentially social creatures, and one could argue, as Walker [34] and others [35] have done, that the social and domestic factors are at least as important in shift work as the biological ones. Certainly, if a shift worker's domestic and social life is unsatisfactory, then the individual will not be coping satisfactorily, however well adjusted the sleep and circadian rhythm factors may be. More usually, however, poor domestic adjustment adversely affects sleep and circadian factors. A common example concerns the childcare and household management tasks that can be expected of a female shift worker. Unlike her male colleagues, she is often expected by her spouse to continue to run the household and can thus find herself completely unable to comply with the routine that good sleep hygiene and circadian adjustment might require. Specifically with regard to the care of children, that issue may be less salient for seniors as their children have often "flown the nest." However, some senior couples start a family relatively late in life and may have teenagers in the home, and others may have grandchild care-giving responsibilities; so the issue is not always moot.

Whether or not domestic issues are potentially disruptive for the senior shift worker, there are still very important social and community disruptions. Shift workers often suffer from social isolation from day-working friends and from religious and community organizations that work under the expectation that evenings or weekends will be free for meetings and activities. Thus, for example, a senior shift worker on the evening shift may find that they are now unable to attend the Wednesday evening Bible study group or bowling league that they had previously enjoyed. One might advance the view that perhaps a shift worker who is denied access to community meetings and social and political associations is as much disadvantaged as a handicapped person who is denied wheelchair access to a museum. Such religious and community activities are often very important in the lives of seniors, and interference by shift work routines may thus be quite profound for them.

Conclusions

There are ever increasing numbers of shift working seniors. Such people are more likely to suffer from sleep disruption than younger shift workers. Although seniors may have fewer problems than younger adults in staying awake at night, they are likely to have more problems in trying to sleep during the morning hours that follow. Unless starting shift work de novo, seniors are also likely to suffer additional coping problems related to the health consequences of shift work. Social factors may also serve to render coping with shift work difficult.

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Part 3
Chapter
14

Sleep disorders in the elderly

Nocturia in the aging population

Ragnar Asplund

Introduction

Nocturia is a highly prevalent disorder, with a profound impact on life expectancy, health, and quality of life. Its prevalence is fairly equal in men and women and shows an age-related increase in both sexes [1].

The prevalence of nocturia increases throughout the whole adult lifespan: two or more episodes of micturition per night occur in 3.4% of men and 3.1% of women of ages up to 30 years, 5.7% of men and 7.2% of women of ages 30 to 59 years, and 32.4% of men and 26.7% of women aged 60 years or older [2]. In the age group 80 years and above, 4 out of 10 men and women have two or more episodes of nocturnal micturition [3].

The occurrence of nocturia and that of nocturnal polyuria are deeply interrelated. In the elderly, an increased number of nocturnal voiding episodes is largely attributable to an increased nocturnal urine output, while in younger people decreased bladder capacity is a more important mechanism in the pathogenesis of nocturia [4]. In the elderly, an increase in nocturnal urine output is involved in three of four cases of nocturia.

Impairment of health and quality of life is more prevalent in elderly people with nocturia than in the elderly in general. Having two or more nocturnal voiding episodes is associated with impairment of health-related quality of life of a degree similar to that in type 2 diabetes [5]. Many elderly people regard nocturia as an inevitable part of normal aging and thus underestimate the extent of the problem, and some doctors share their misconception [6].

There are numerous medical conditions that are associated with increased nocturnal voiding, such as cardiac diseases, diabetes, obesity, edemas of different origins, and sleep apnea. Also different kinds of medications, for example analgesics and diuretics, increase the propensity to nocturia. In a recent study comprising 1872 men and women with nocturia, a logistic regression analysis revealed that the odds of having nocturia increased with age ($p < 0.001$) and with increasing body mass index (BMI) ($p < 0.001$) and were higher if the respondent had type 2 diabetes (odds ratio[OR] 1.67, 95% confidence interval [CI] 1.20–2.33) or cardiac disease (OR 1.37, 95% CI 1.01–1.87), or used diuretics (OR 1.38, 95% CI 1.08–1.75) [7].

In view of the relationship between different somatic diseases and nocturia it might be expected that nocturia will be associated with increased mortality rates. But even after adjustment for the influence of heart diseases, stroke, and diabetes it was found in an earlier study that there was still a 34% increase in the risk of death in elderly men and women with three or more nocturnal voiding episodes [8]. A considerable part of this excess mortality could be linked to fall injuries.

In parallel with increased nocturnal voiding there is an increase in different somatic symptoms such as muscle cramps in the calves, leg tinglings, and nocturnal sweating [9]. As nocturia is often caused by nocturnal polyuria, persons afflicted with these symptoms may also be troubled by consequences of a negative fluid balance at night in the form of giddiness when standing up, and as a result they are at increased risk of sustaining fall injuries.

Nocturia and sleep

The sleep–wake cycle and the 24-hour rhythm of the body temperature are regulated by a circadian periodicity that originates from the suprachiasmatic nucleus in the hypothalamus. In the morning we wake up, our body temperature increases from the nocturnal level and we are able to be active throughout the day. In the late evening, when it is dark, we normally go to bed and after a while we fall asleep. The 24-hour rhythm of life processes can also be found in the cyclic variation of urine output, with higher levels in the daytime than at night. This inhibition of the nocturnal diuresis is sleep protective. In a minor proportion of

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elderly people diurnal rhythm of urine output is weak or absent, a consequence of impairment of the rhythmicity of the vasopressin incretion, resulting in increased nocturnal urine output and, consequently, nocturia [9, 10].

Elderly people with nocturia are troubled with a considerable morbidity resulting from sleep disruption. Perception of poor sleep (Figure 14.1), frequent awakenings, difficulty in falling asleep after nocturnal awakenings, and increased nightmares and consequently by the feeling of having slept too little are all increased by nocturnal voiding. Lying awake in bed more than half of the night is twice as common in elderly men with three or more nocturnal micturition episodes than in those with no nocturnal voids (7.8% vs. 3.7%) and, correspondingly, seven times increased in elderly women (14.3% vs. 2.4%). Total night's sleep decreases in both sexes in parallel with increasing nocturnal voiding [9].

Diagnostic considerations in nocturia

The International Continence Society (ICS) has defined nocturia as "the complaint that the individual has to wake at night one or more times to void." Also included in the definition is that "each void is preceded and followed by sleep" [11]. Nocturia is present in elderly persons (≥65 years) if the nocturnal part of the 24-hour voided volume exceeds one-third of the total. "Night" is most often defined as the period of time from going to bed with the intention to sleep to getting up in the morning with the intention of staying out of bed. For practical reasons nocturia is most often considered to occur if there are two or more nocturnal voids per night, as one nocturnal void is in most cases considered acceptable and associated with no or only minor influence on sleep and well-being.

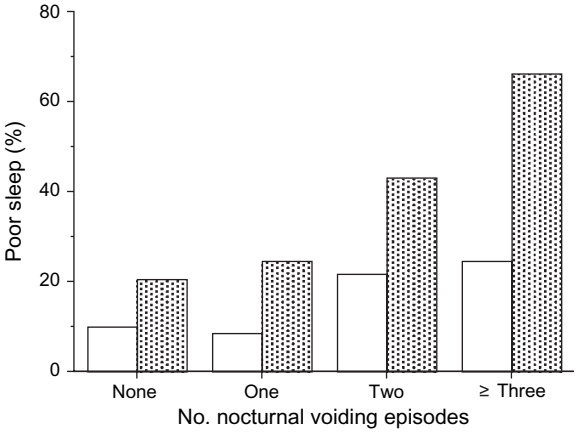

Figure 14.1. The occurrence of poor sleep (%) in men (white bars) and women (shaded bars) with different numbers of nocturnal voiding episodes [9].

On the basis of analyses of information collected from frequency–volume charts (records of micturition episodes and voided volumes in the daytime and at night), the pathophysiological conditions underlying nocturia can be categorized as: nocturnal polyuria, a low nocturnal bladder capacity, or a combination of the two [4]. In the elderly nocturnal polyuria has been stated to occur if the nocturnal urine output exceeds one-third of the 24-hour urine volume [11]. With a 72-hour frequency–volume chart most people with nocturia can be correctly placed in these categories [12].

In elderly individuals with no nocturnal voiding episodes, but with voiding in the morning, the urine output during the day is twice as high as that in the night. The larger the number of voiding occasions during the night the greater the nocturnal proportion of the 24-hour diuresis [9]. In a large study comprising men and women of ages 60–80 years it was found that among individuals with two or more nocturnal voids, nocturnal polyuria occurred in 55%, which was a far higher figure than in those with no more than one nocturnal void [12].

Nocturia in relation to certain diseases and symptoms

Fall injuries

The prevalence of hip fractures during a 5-year period is twice as high in elderly men and women with three or more nocturnal voiding episodes compared with those without nocturnal voiding (Figure 14.2) [13]. Falls and fractures during the visits to the toilet and back are the most serious consequences of nocturia, especially in older, frail people with impaired cognitive and motoric functioning. In a study of night-time falls in the elderly, it was found that the occurrence of two or more nocturnal voids was associated with a two-fold increase in such falls compared with fewer than two such voids [14]. The consequences of fall injuries in the elderly are often serious with respect to life expectancy, health, functional ability, and quality of life.

In an epidemiological study covering a time period of 4.5 years and comprising more than 6000 elderly men and women, the overall death rate was twice as

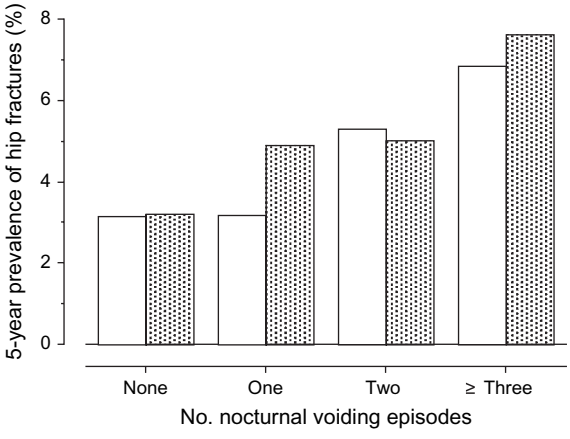

Figure 14.2. The 5-year prevalence (%) of hip fractures in men (white bars) and women (shaded bars) in relation to the number of nocturnal voiding episodes [13].

high in both men and women with ≥3 nocturnal voids as in the whole groups of men and women, respectively, and the difference remained after the influences of age, cardiac diseases, diabetes, and stroke had been taken into account (Figure 14.3) [8]. Persons who had had ≥3 episodes of nocturnal micturition and had died during the study period showed some differences in their reports of symptoms at the start of the study compared with the group with ≤2 nocturnal micturition episodes. Giddiness and poor balance in the daytime had been about twice as common in both men and women, and dry mouth in women, in the former group. Nocturnal drinking was also more common in parallel with increased nocturnal voiding. Hence, increased nocturnal voiding was associated with symptoms indicative of a negative fluid balance. The raised mortality rate in elderly people with nocturia may therefore be a consequence of increased falling, partly as a result of orthostatic reactions during nocturnal rising and walking to the bathroom and back [8].

In one study, hip fracture was found to lead to permanent institutionalization in every seventh patient who had been able to live at home at the time of the fracture, and this development caused significant impairment of the patient's functional capacity. Loss of ability to walk outdoors, an increased need for help from others, and a general loss of autonomy are common consequences of hip fractures [15].

In parallel with the growing number of elderly people in western countries, the number of hip fractures has increased considerably during the last two decades [16] and is resulting in large societal costs [17].

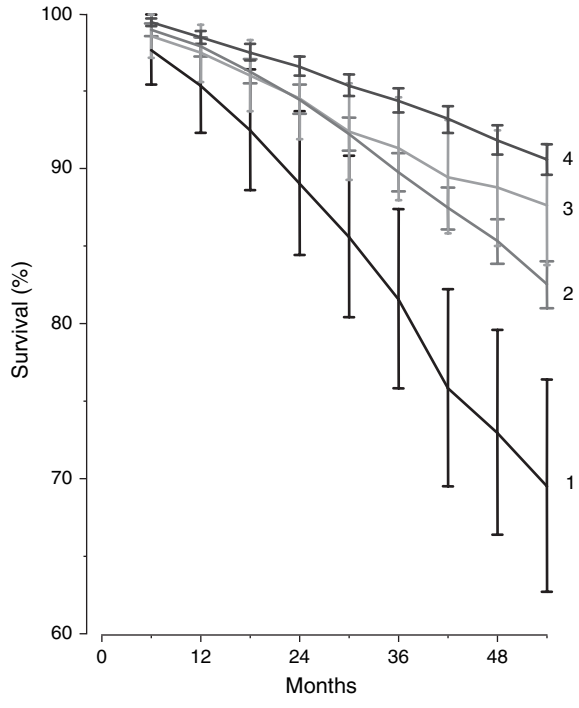

Figure 14.3. Survival curves (mean and 95% confidence interval) of men with three or more nocturnal voiding episodes (1), the whole group of men (2), women with three or more such episodes (3), and the whole group of women (4) [8]. See plate section for color version.

For example, in the Italian population aged ≥45 years, the numbers of hospitalizations following hip fracture and acute myocardial infarction (AMI) between 1999 and 2002 were comparable, while the direct costs of hip fractures were higher and grew faster than the costs for AMI. The authors conclude that hip fractures in Italy are a serious medical problem and a leading health-cost driver [17].

Furthermore, a comparison of the outcome of hip fracture surgery in Italy in the periods 1978–1983 and 1998–2003 showed that there was no significant temporal improvement either in mortality, or in quality of life [16]. Hence, taking into account the increased risk of disability, along with the huge financial costs, no effort should be spared to reduce the risks of falling in the elderly, including to a large extent, the major risk factors nocturia and nocturnal polyuria.

Visual impairment is a condition of particular importance in this connection. Poor sleep, frequent awakenings, and difficulties in falling asleep after waking at night are all more common in both sexes [18]. A probable explanation may be that visual impairment is accompanied by difficulties in establishing a normal 24-hour rhythm. Consequently, nocturia is increased

by a lack of nocturnal inhibition of nocturnal urine output [19].

Visual impairment and sleep impairment contribute independently to increased nocturnal micturition [18]. Among men and women with both visual impairment and poor sleep, self-reports of three or more nocturnal micturition episodes were three times and four times more frequent, respectively, than among men and women with good vision and good sleep [19]. It must be concluded that there is a considerable additional risk of falls and fractures in nocturic elderly people with visual impairment, as an obvious consequence not only of the visual impairment in itself, but also of the associated poor sleep and increased nocturnal voiding.

Nocturia and the obstructive sleep apnea syndrome

In the obstructive sleep apnea syndrome, a strong intrathoracic negative pressure is generated by attempts at forced inspiration against a closed glottis. The low intrathoracic pressure leads to an increase in the return of blood to the thorax through the central venous system, which in turn causes dilatation of the right atrium of the heart. This results in increased secretion of atrial natriuretic peptide (ANP) from the heart to the systemic blood circulation [20]. The increased circulating ANP level leads to an increase in nocturnal diuresis, which in such cases can be normalized with continuous positive airway pressure (CPAP) [21].

Nocturia, thirst, and mucous membrane symptoms

Nocturia and thirst

Although thirst is a rather uncommon symptom in the elderly in general, it is a common finding in elderly persons with nocturia. In the previously described questionnaire survey of nocturia and somatic symptoms in an elderly population in northern Sweden, the statement "I am often thirsty" was answered affirmatively by 17.4% of the men and 10.5% of the women with no nocturnal voids. The corresponding frequencies in men and women with three or more nocturnal voids were 46.3% and 34.5%, respectively. In those who had no nocturia, thirst was most often experienced in the daytime, and only 3.5% of the men and 2.8% of the women were troubled by thirst at night. In parallel with an increasing number of nocturnal voids an increasing proportion of men and women reported that they were most troubled by thirst at night. And, consequently, the statement "I often get up to drink at night" was answered affirmatively by 4.4% of the men and 8.7% of the women with no nocturnal voids and in 34.6% and 40.7% of the men and women with three or more nocturnal voids [9].

Not only toilet visits but all occasions of getting out of bed at night are associated with an increased risk of fall injuries. Therefore, all kinds of sleep-disturbing symptoms should receive attention and be treated if possible, and thirst and drinking at night seem to be disregarded as underlying mechanisms of fall injuries.

Nocturia, dry eyes, and dry mouth

Both dry eyes and dry mouth are common complaints in the elderly. In a questionnaire survey in 2481 people, aged 65 to 84 years, 27% reported that they had dry eyes or dry mouth often or all the time and 4.4% reported the occurrence of both [22]. Although there is an increased prevalence of glandular hypofunction resulting in dryness of the mucous membranes in persons with inflammatory diseases, especially rheumatoid arthritis and Sjögren's syndrome, many persons with dry eyes and/or dry mouth show no atrophy in the salivary or lachrymal glands [23].

In a questionnaire investigation among elderly men and women, dryness of the eyes was reported by 14.3% of the men and 21.7% of the women. Dryness of the mouth occurred in 25.1% of the men and 36.3% of the women and showed an age-related increase in both sexes [3]. Increased nocturnal micturition was associated with a stepwise increase in dryness of the eyes and the mouth in both men and women. The occurrence of dry eyes was three times more common, and the occurrence of dry mouth and throat was four times more common in persons with three or more nocturnal voids than in those with no nocturnal voids after adjustment for age, sex, and the use of analgesics and diuretics. A reasonable interpretation of the increased dryness of the mucous membranes is that nocturia, often a consequence of increased nocturnal urine output, generates a negative fluid balance [3].

Nocturia and burning mouth syndrome

One condition with a profound impact on sleep is burning mouth syndrome (BMS) [24]. This is characterized by a burning pain in the tongue or other oral

mucous membranes, usually in the absence of clinical and laboratory findings, and is a fairly common complaint [25]. In a questionnaire survey among randomly selected men and women of ages 20–69 years in northern Sweden, the prevalence of BMS was found to be 1.6% in the men and 5.5% in the women. The prevalence increased with increasing age [26].

In the elderly, BMS is more common in women than in men, and in women there is a stepwise increase in BMS in parallel with an increase in the severity of nocturia. Sleep impairment is common in men and women with BMS and is further aggravated by increasing nocturnal voiding. The occurrence of frequent awakenings, nightmares, and awakenings with anxiety is correspondingly increased [25].

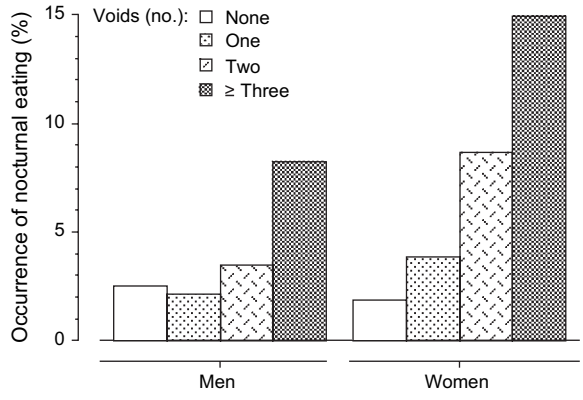

Figure 14.4. The occurrence of nocturnal eating (%) in men and women with different numbers of nocturnal voiding episodes [28].

Nocturia, obesity, and nocturnal eating

During recent years the relationship between overweight and symptoms from the urinary tract has attracted increasing interest. As the coexistence of obesity and urinary tract symptoms is common in society, particularly in the elderly, and as life expectancy is increasing, an increasing number of elderly people will be affected by these two conditions. The interaction between them is therefore an important area for research.

The prevalence of nocturia has been found to increase in parallel with an increasing body mass index after adjustment for a number of possible confounders [27]. In a recent questionnaire survey in Finland comprising 1726 men and 2003 women aged 43.5 ± 15.3 (mean ± SD) and 42.0 ± 15.7 years, respectively, it was found that obesity was associated with increased nocturnal voiding, and more so in women than in men [28].

In a study of elderly men and women without or with different degrees of nocturia, wakening by hunger was common in 1.0% of the men and 2.4% of the women with no nocturia. Awakenings for that reason were five times more common in men and six times more common in women with three or more nocturnal voids than in those with no such voids [27]. The habit of nocturnal eating (Figure 14.4) and the occurrence of poor appetite in the daytime, well-known symptoms of the so-called nocturnal eating syndrome, increased in parallel with an increasing number of nocturnal micturition episodes in both men and women [27]. These findings seem to support the idea that nocturia increases the risk of obesity through its propensity to impair sleep.

It has been suggested that nocturia is a consequence of obesity, which seems to be a reasonable assumption, as body weight is often increased in persons with sleep apnea, a condition with nocturia and nocturnal polyuria as prevalent symptoms [28]. However, the order of cause and effect might also be the reverse. The length of uninterrupted sleep period to the first nocturnal awakening is about 2 hours shorter in persons with frequent nocturnal voiding [27]. Recent studies have shown that sleep impairment is associated with a substantial risk of obesity. During normal sleep the level of ghrelin, a "hunger-inducing" hormone that is produced in the stomach and gut, is low. Sleep impairment is associated with increased levels of ghrelin, and thereby stimulates eating behavior. The sometimes profound sleep deterioration in association with nocturia should be considered in this connection [29]. Elderly persons with nocturia have an increased propensity for nocturnal eating and a reduced appetite in the daytime, findings that may support the view that overweight is increased as a consequence of nocturia [27].

Increasing body weight is one of the most threatening health-related conditions in global public health, and all possible efforts should be made to promote weight reduction, which in turn will reduce the risk of metabolic syndrome, cardiovascular diseases, and diabetes. Improvement of nocturia has a favorable influence on sleep and may therefore be helpful in the prevention of obesity.

Nocturia and depression

Increased prevalence rates of depressive symptoms have been reported in association with lower urinary tract

symptoms [30]. In a study on the connection between nocturia and depression in men and women of ages 18 years and over (2048 persons, response rate 69.8%), the Major Depression Inventory [31] and reports on sleep and nocturnal voiding were included in a questionnaire. In a multiple logistic regression analysis with major depression, health (poor vs. good), and age as independent variables, the probability of having nocturia, defined as ≥2 episodes per night, was increased 6.5(2.6–15.6) times in men and 2.8(1.3–6.3) times in women who met the criteria of major depression [32].

The underlying mechanism is multifactorial. One probable reason for increased nocturnal voiding in association with depression may be that sleep is more superficial and fragmented in depression than in normal persons, resulting in an earlier perception of bladder distension with a consequent need to void, and also that the sleep-dependent inhibition of urine secretion is absent. In depression there are also disturbances in the vasopressin system, resulting in increased nocturnal diuresis [32].

Treatment of nocturia

Non-pharmacological treatment

As mentioned in the introduction section there are numerous clinical conditions with an increased risk of nocturia in an elderly population, such as cardiac diseases, diabetes, obesity, edemas of various origin, and sleep apnea. These conditions should be treated as appropriately as possible before more specific treatment of nocturia is considered. Coffee and tea, particularly in the evening, should be reduced or avoided if it is suspected that they may be a cause of nocturia (there is no better method available than to test whether this works for a few nights). Concerning smoking, there are conflicting reports. Nicotine increases the circulating level of antidiuretic hormone, but for only a short while, and the increase in nocturia observed in some cases may be a consequence of a rebound effect. (As smoking is harmful for health in many other ways, there is always good reason for advising people not to smoke.) Improvement of nocturia has also been attributed to physical activity, but there seem to be only few and inconclusive data in this field so far.

Fluid restrictions are often advised to elderly people with nocturia, and in certain cases these may be effective. In some people, however, an increased frequency of nocturnal voiding is caused by a disturbance of the vasopressin system. They avoid drinking in the evening, but are unable to resist the impulse to drink during the night. In such cases self-imposed fluid restrictions before bedtime are not effective in reducing the nocturnal urine output, and may even be harmful for several reasons [9, 33]. Many elderly people who restrict their fluid intake run a risk of suffering unnecessarily from thirst and concomitant symptoms such as constipation and dryness in the mucous membranes of the eyes, respiratory tract, and urogenital organs [3, 9, 33].

Treatment of nocturnal polyuria

Desmopressin

Desmopressin, a synthetic analog of the antidiuretic hormone vasopressin, has been used since the early 1960s for diabetes insipidus and from the early 1980s in the treatment of nocturnal enuresis in children. Since the finding that nocturnal polyuria is a common feature in nocturia [34, 35], desmopressin has also been shown to be useful in the treatment of nocturia of polyuric origin in the elderly. The first reports of this effect were published in 1993 [36].

Treatment with desmopressin in the evening, even in low doses, has been proven effective in reducing the number of episodes of nocturnal micturition. In a study of 30 elderly men and women of ages 75.4 ± 6.6 years (mean ± SD) with three or more micturition episodes per night and nocturnal polyuria that was treated with oral desmopressin 0.1 mg at bedtime for 4 weeks, the nocturnal urine output was almost halved, from 955 ± 255 to 522 ± 210 mL ($p < 0.0001$) The number of nocturnal voiding episodes was reduced from 5.20 ± 1.16 to 2.24 ± 1.12 ($p < 0.0001$) [37].

In a long-term study of the effect of desmopressin on nocturia in patients who in a short-term study had shown that they responded to desmopressin, an optimal desmopressin dose (0.1, 0.2 or 0.4 mg orally) for 10–12 months resulted in a decrease in the number of nocturnal voiding episodes by half and was well tolerated in most cases. Clinically significant hyponatremia occurred in 1% of the cases [38].

Diuretics

Diuretic drugs, most often taken in the morning, are associated with a two-fold increase in nocturia [39]. This can result in increased thirst, leading to an increased fluid intake in the daytime and consequently increased nocturnal urine output. If furosemide is taken 6 hours before going to bed, the nocturnal

diuresis, and accordingly the nocturia, can be reduced [40]. In a randomized, placebo-controlled trial comparing night-time doses of placebo and 1 mg of bumetanide, the bumetanide treatment decreased the number of nocturnal micturition episodes by 25% compared with placebo [41].

Treatment of nocturia in low bladder capacity

Nocturia is one of the symptoms of a low bladder capacity. Normally the bladder capacity is about one-third larger at night than in the daytime, but if the bladder capacity is reduced for some reason, this will result in increased nocturnal voiding [9]. Few clinical trials have specifically addressed the use of medications for treating nocturia through improvement of bladder capacity.

Antimuscarinic drugs are most commonly used for treatment of overactive bladder and consequently of nocturia as one of its symptoms. Side effects may include constipation, dry mouth, and cognitive impairment. Antimuscarinic drugs act by depression of both voluntary and involuntary bladder contractions. They can reduce nocturnal micturition by blocking the muscarinic receptors on the detrusor muscle, thereby reducing the ability of the bladder to contract, or by increasing the bladder capacity by decreasing urge during the storage phase [42].

There are five subtypes of muscarinic receptors (M1–M5) in the human bladder. On the detrusor muscle cells, M3 receptors are mainly responsible for the micturition contraction. Antimuscarinic drugs can be divided into two groups with reference to their chemical structure and physiological properties: tertiary amines (including darifenacin, propiverine, solifenacin, tolterodine) and quaternary amines (oxybutynin, propantheline, trospium). In contrast to tertiary amines, which are well absorbed from the gastrointestinal tract, the quaternary amines can be absorbed to only a minor extent [42].

In general, antimuscarinic drugs are well tolerated. Side effects may include, in order of decreasing prevalence, dry mouth, constipation, and cognitive impairment. One serious, but less common, side effect of antimuscarinic medication is cardiac dysfunction, which may include ventricular tachycardia. Adverse effects deriving from the central nervous system have been observed in the elderly, with impairment of memory and sleep, and occurrence of hallucinations, confusion, and delirium; these are more probable when tertiary amines are used [42, 43, 44].

The evidence base for the use of antimuscarinic drugs has not been established for treatment of nocturia specifically, but the appropriateness of these drugs has been investigated in studies on the overactive bladder syndrome (OAB), in which nocturia is a common symptom.

Nocturia and benign prostatic obstruction

Decreased nocturnal voided volumes and a consequent increase in nocturia may be indicative of bladder outlet obstruction or of detrusor overactivity [45]. Both of these mechanisms may be present in elderly men with benign prostatic hyperplasia (BPH). Neurological disturbances of the detrusor that may involve activation of the muscarinic receptor system and changes in the central nervous system may also play a role in the development of detrusor overactivity.

Alpha-1-antagonists, such as alfuzosin and doxazosin, are used for alleviating irritative and obstructive symptoms associated with BPH. As in association with antimuscarinic compounds, only very sparse reports have focused on nocturia in connection with alpha-1-antagonist treatment, although the results of such treatment appear to be good in comparison with those of other kinds of medication. In a 2-year study of men with BPH, it was found that the occurrence of three or more nocturnal voiding episodes was reduced by two-thirds [46].

Testosterone 5-α-reductase inhibitors (finasteride and dutasteride) are often prescribed to men with BPH with the aim of reducing a need for surgical treatment and of alleviating acute urinary retention, and they are often helpful in such situations. Only a few studies have addressed nocturia. In a study of 1229 45- to 80-year-old men, with BPH and with a mean of 2.5 nocturnal voiding episodes at the start of the study, nocturia was reduced by half in 25% of the men [47].

Nocturia in elderly women

Estrogen deficiency, a common consequence of the menopausal transition, causes atrophic changes within the urogenital tract and is associated with nocturia [48]. Estradiol or estriol is often tried for relief of urogenital symptoms. Low-dose vaginal estradiol has been found to be the most efficacious regarding relief of such symptoms, but has no influence on nocturia [49].

Tibolone is a compound used for alleviating menopause-related symptoms. Its metabolites show estrogenic, gestagenic, and androgenic properties. In a placebo-controlled, double-blind, randomized,

multicenter study among 396 healthy post-menopausal women experiencing a minimum of seven moderate to severe hot flashes per day (60 per week), it was found that tibolone 2.5 mg significantly reduced nocturia compared with placebo during a 3-month study period [50].

Conclusions

Nocturia has a detrimental influence on life expectancy, health, and overall quality of life. Elderly persons with nocturia are troubled by sleep impairment in the form of involuntary awakenings, nightmares, and a general feeling of insufficient and non-restorative sleep. Consequently they are troubled by increased daytime sleepiness and a need for napping. Nocturnal muscle cramps in the calves, leg tinglings, and nocturnal sweating are also increased in parallel with increasing nocturnal voiding.

Falls and fractures during the visits to the toilet and back are the most serious consequences of nocturia. As nocturia is often caused by nocturnal polyuria, a negative fluid balance at night increases the risk of giddiness when standing up, with a consequently increased risk of fall injuries. The negative fluid balance also leads to increased dryness of the mucous membranes in the eyes and the respiratory tract. Thirst, particularly at night, is frequently reported by elderly persons with nocturia. The need to get up to drink at night may represent an additional risk factor for falling, besides the nocturnal micturition in itself. Nocturnal eating with consequent overweight is also increased in cases of nocturia.

Nocturia may be attributable to nocturnal polyuria (nocturnal urine overproduction), a diminished nocturnal bladder capacity, or a combination of the two. A disorder of the vasopressin system, with very low or undetectable levels of vasopressin at night and in some cases throughout the entire 24-hour period, affecting some elderly people may cause an increase in the nocturnal urine output, which in the most extreme cases accounts for 85% of the 24-hour diuresis. Self-imposed fluid restrictions before bedtime are not effective in reducing the nocturnal urine output in this condition. The increased urine output can be treated with desmopressin orally at bedtime, in generally low doses.

Nocturia is also more prevalent in association with a reduced bladder capacity. Normally, in both men and women, the bladder capacity is about one-third larger at night than in the daytime. This variability in bladder capacity has a protective effect on sleep. Antimuscarinic drugs are used with the aim of depressing involuntary bladder contractions. Decreased nocturnal voided volumes in men, with a consequent increase in nocturia, may suggest either difficulty in emptying the bladder or detrusor overactivity. Alpha-1-antagonists and 5-α-reductase inhibitors are often prescribed to men with symptoms indicative of BPH.

In women, estrogen deficiency, a common consequence of the menopausal transition, causes atrophic changes within the urogenital tract. Consequently women with such deficiency are more prone to urogenital symptoms, including nocturia. Estrogen treatment has been shown to have a favorable influence on urological symptoms in general, but studies indicating a specific effect on nocturia are lacking. Tibolone, a compound with metabolites showing estrogenic, gestagenic, and androgenic properties, has been shown to improve nocturia at least during a 3-month treatment period.

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Part 3
Chapter
15

Sleep disorders in the elderly

Sleep and fibromyalgia in the elderly

David S. Hallegua and Daniel J. Wallace

Introduction

Sleep is a vital physiological process with important restorative functions. Although many qualitative and quantitative changes in sleep occur with age, many sleep-related disorders also occur with increasing frequency among elderly people [1]. Physicians often do not diagnose these conditions and the symptoms are thought to be due to co-existent medical illness. Fibromyalgia syndrome (FM) is a form of non-articular rheumatism, which is thought to affect between 2% and10% of the adult population. It was given very little importance until Smythe and Moldofsky demonstrated specific sleep abnormalities and classification criteria were established as a result of a large multicenter trial under the auspices of the American College of Rheumatology [2, 3]. Among other symptoms, sleep pathology is a universal feature of the syndrome and improvement in sleep architecture is often the cornerstone of effective therapy.

Historical references to FM

Widespread pain associated with insomnia has been described from biblical times in the books of Job and Jeremiah and in modern times in industry workers and war-scarred victims [4]. Various terms were used to describe this malady including neurasthenia and "fibrositis" until the absence of inflammation in the muscle was proven by biopsy. Hugh Smythe and Harvey Moldofsky from the University of Toronto described alpha wave intrusion into delta wave sleep on polysomnograms and correlated it with the presence of tender points [2]. Muhammad Yunus *et al.* statistically correlated tender points with fatigue, functional bowel disease, sleep pathology, tension headache, and other systemic symptoms in 1981 [5]. The classification criteria published by the American College of Rheumatology allowed epidemiological surveys to establish the prevalence of FM but it is well established that there are many patients with FM with fewer than the requisite 11 tender points that have bonafide FM (Figure 15.1).

Epidemiology

Population-based studies done using the 1990 American College of Rheumatology criteria by Wolfe *et al*. and White *et al.* showed that FM had a prevalence of about 2–4.2% and was 8 to 9 times more prevalent in women than in men [6, 7]. The prevalence increases with aging and is between 8% and 9% in women between 50 and 79 years of age. Thus, FM is of particular importance in the geriatric population. A geriatric clinic study recruiting consecutive patients found the prevalence of FM to be 9.2% and about 41% in Caucasians [8]. The demographic data in this study of FM patients who were older than 60 years showed that FM patients were more likely to be female and have lower levels of education compared to the non-FM geriatric clinic patients. Approximately 6 million people in the United States have FM (2% of the adult population), and another 6 million have FM-related complaints but

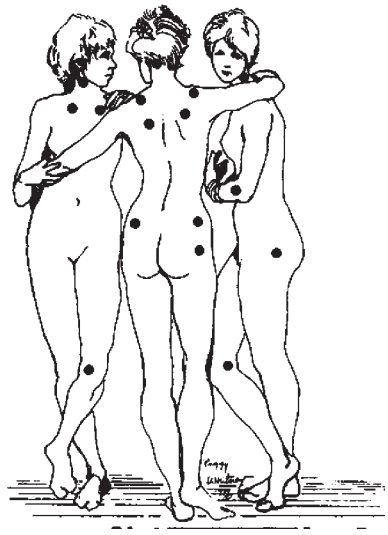

Figure 15.1. The 1990 American College of Rheumatology criteria for fibromyalgia. Updated and revised from Wallace DJ, Wallace JB. *All About Fibromyalgia*. New York/London: Oxford University Press; 2003, with permission.

Principles and Practice of Geriatric Sleep Medicine. ed. S.R. Pandi-Perumal, J.M. Monti, and A.A. Monjan.
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never seek medical attention for it (termed community fibromyalgia).

The etiopathogenesis of fibromyalgia

Primary fibromyalgia is not associated with any other illness whereas secondary fibromyalgia usually is associated with an underlying infectious process, untreated inflammatory arthritis, a repetitive trauma, or a motor vehicle accident. Most of these individuals have pre-existing risk factors such as lower socioeconomic status, psychosocial stressors, poor sleep habits, or myofascial pain syndrome.

Multiple studies including neuroimaging studies have consistently shown that FM pain emanates from changes in the brain and spinal cord using the same mechanism that makes sunburnt skin sensitive to light touch. These changes do not reverse themselves in FM compared to other normal painful conditions.

In FM, thin non-myelinated C-fibers and large myelinated A-delta fibers in the skin are activated and stimulate the dorsal nerve ganglion of the spinal cord constantly resulting in a "wind up" of the nerve cells in the substantia gelatinosa leading to central sensitization [9, 10]. This sensitization occurs via the secretion of increased amounts of substance P and excitatory amino acids (e.g. glutamate), which activate NMDA (*N*-methyl *D*-aspartate) receptors enhancing electrical depolarization and causing calcium influx into nerve cells and making them more excitable [11]. The brain normally inhibits the actions of the pain transmitting neurons in the spinal cord via neurotransmitters such as dopamine, norepinephrine, epinephrine, serotonin, and opioids in the descending tracts into the spinal cord. However, serotonin levels are documented to be low in the cerebrospinal fluid in FM suggesting dysfunction of the descending system [12].

The role of sleep in the etiopathogenesis of fibromyalgia is underscored by the fact that up to 90% of FM patients have non-restorative sleep [13, 14]. The sleep is characterized electrophysiologically by an alpha intrusion pattern on delta wave sleep and clinically as non-restorative sleep. In the elderly population, there is evidence of a decrease in amplitude and duration of slow wave sleep, and a decrease in duration and frequency of eye movements in rapid eye movement sleep [15]. Decreased secretion of growth hormone also occurs with aging and lack of slow wave sleep, which increases muscle deconditioning [16]. Leg cramps increase with aging and increased sympathetic activity may be associated with leg movement disorders such as nocturnal myoclonus or restless legs syndrome [17, 18].

Clinical overview

Diagnostic criteria for FM have not been established and criteria developed for classification is often applied for the diagnosis of an individual patient. The classification criteria require the presence of widespread body pain for at least 3 months in all 4 quadrants of the body including the spine and also the presence of at least 11 of 18 specified tender points [19]. Fibromyalgia can exist with less than 11 tender points and therefore these criteria are not sensitive enough to pick out all cases of FM. Sometimes the presence of fewer FM tender points is termed myofascial pain syndrome, or regional myofascial pain.

The key feature of FM is pain due to central sensitization, which is an exaggeration of sensory stimuli and the perception of touch and pressure as pain [20, 21]. Although the above classification criteria help to classify and establish the diagnosis of fibromyalgia there are many other common clinical symptoms, which contribute significantly to the syndrome's morbidity and are important to address therapeutically. The principal symptoms and signs of FM are listed in order of prevalence in Table 15.1.

Table 15.1. Prevalence (%) of frequently observed symptoms and signs in fibromyalgia

Symptom or sign	Percentage
Widespread pain with tender points	100
Muscle and joint aches	80
Non-restorative sleep	80
Fatigue	60
Tension headache	53
Dysmenorrhea	40
Irritable colon	40
Subjective numbness, tingling	35
Livedo reticularis	30
Complaints of fever	20
Complaints of swollen glands	20
Significant cognitive impairment	20
Restless legs syndrome	15
Irritable bladder	12
Chronic pelvic pain	5

Sleep disturbances are a common problem in the elderly FM patient and include a delay in sleep onset unlike the usual phase shift that occurs in the elderly with the older patient usually sleeping earlier and waking earlier [22]. There is also poor maintenance of sleep and non-refreshing sleep present, which frequently leads to the patient staying in bed longer and waking well into the early afternoon. Sleep-associated movement disorders such as nocturnal myoclonus and restless legs symptoms are seen in 30–50% of patients. Elderly FM patients who are obese may suffer from obstructive sleep apnea and need to have a sleep study to diagnose and treat this condition [23].

Fatigue is present in over 80% of patients with FM and can impair the elderly patient's ability to exercise and function. It results in decreased mental and physical endurance. Other causes of fatigue such as heart failure, emphysema, hypothyroidism, and inflammation must be excluded as potential causes of fatigue.

Cognitive, memory, and psychological disturbances include short-term memory impairment and inability to concentrate or multi-task; sensory and cognitive overload are common as side effects of medications or due to an evolving dementia or cerebrovascular disease. Patients with FMS often exhibit symptoms of autonomic dysfunction due to altered sympathetic and parasympathetic function. Neurogenic hypotension causes dizziness, near syncope, syncope, and vertigo, and can be evaluated with a tilt table test [24]. Dry eye and mouth, which are common with aging and diabetes, is present in about 30% of FMS patients and may test false positive on a Schirmer's test. However, autoantibodies for Sjogren's syndrome are absent. Bladder and bowel disturbances include pain, which is present during urination and when the bladder is full, urge, and stress incontinence. Bowel symptoms include pain, which may be constant or colicky and may be present in any quadrant. Hypersensitivity of the bowel due to irritable bowel syndrome is thought to be responsible for the pain and may co-exist with constipation and diarrhea. Abdominal bloating after eating can be seen and may be due to the presence of bacterial overgrowth in the small intestine [25]. Neurological symptoms can be due to shortening of muscles and compression of nerves that result in atypical patterns of numbness, tingling, and swelling. Hyper-reflexia is common in FMS but it is rarely associated with a cervical myelopathy. MRI imaging of the cervical spine is necessary to exclude this possibility [26].

Some patients complain of fevers due to an autonomic or hormonal imbalance but in the elderly FM patient, true fever is important to ascertain due to the similar confusing symptoms of polymyalgia rheumatica (PMR) [27]. Fibromyalgia patients have tenderness in their muscle regions without inflammation, weakness or myositis. The most tender areas are in the neck, upper back, anserine bursa, proximal hip, and shoulder girdle region, which is similar in distribution to PMR. Similarly, joint discomfort or stiffness is common, always without synovitis unlike PMR. Tension headaches, anxiety, and aggravation of symptoms by changes in weather, poor sleep, and tension are more common in the younger patients than in older patients with FM. In the study by Gowin on geriatric patients with FM, the patients were significantly less likely to be active and have lower health satisfaction scores [22]. They had higher levels of depression on a Geriatric Depression Scale and more disability on the Health Assessment Questionnaire than the non-FM geriatric clinic patients. The majority of FM patients have a history of depression, but only 18% are depressed at any given visit [28]. Individuals with FM tend to have more anxiety, poorer coping skills, and psychosocial stressors than control populations.

Association with other central sensitization syndromes and other illnesses

Patients with FM-like complaints often have other conditions associated with central sensitization. A listing of these and their prevalence in FM and their association with FM associated conditions is found in Table 15.2 [29, 30]. Chronic fatigue syndrome has its own statistically validated criteria, but differs from FM in that fatigue is more prominent than myofascial discomfort and many more chronic fatigue patients had documented evidence that an infectious process induced their symptoms. There is considerable overlap between FM and conditions associated with visceral hyperalgesia such as irritable bowel syndrome, noncardiac chest pain, non-ulcer dyspepsia, and esophageal spasm. Dysmenorrhea, chronic pelvic pain, vulvodynia, vaginismus, interstitial cystitis, and irritable bladder are found in a minority with FM. Other regional (not necessarily four quadrant) associated syndromes include repetitive strain, temporomandibular joint dysfunction, and scoliosis.

In elderly patients with FM, a significant disease association was found by Gowin *et al*. with coronary

Table 15.2. Fibromyalgia (FM) associated conditions

Condition	Percentage with FM	Percentage with FM-associated conditions
Chronic fatigue syndrome	50	50
Functional bowel spectrum	20	40
Autoimmune disease	10	2
Lyme disease	30	2
Reflex sympathetic dystrophy	100	1
Irritable bladder	10	12
Chronic pelvic pain	50	5
Tension headache	20	53
United States population	2	–

artery disease (OR – 3.6, 95% CI 1.0, 12.6) [22]. The authors postulate that FM patients with coronary artery disease were likely to be less active and have disturbed sleep because they took beta-blockers more often than their non-FM geriatric counterparts. The association of geriatric FM with the use of acetaminophen (OR – 4.7, 95% CI 1.4, 16.1) suggests that a prevalent illness such as osteoarthritis causing pain and disrupting sleep might be important in the pathogenesis of FM in the elderly. Association of stroke, asthma, and use of prednisone and calcium with FM in elderly patients was suggestive but not statistically significant.

Clinical evaluation and differential diagnosis

Fibromyalgia patients have normal blood chemistry panels, complete blood counts, immune profiles, imaging studies, and electrodiagnostic testing. It is often a diagnosis of exclusion. Many individuals diagnosed with FM turn out not to have the syndrome. Other disorders and conditions are associated with myofascial symptoms and need to be differentiated from FM. These include multiple sclerosis, hypothyroidism, rheumatoid arthritis, bipolar illness, allergies, nutritional deficiencies, anorexia, cancer, substance (e.g. steroid, alcohol, heroin, cocaine) withdrawal, and opportunistic infections. The elderly patient with FM is more prone to be diagnosed with polymyalgia rheumatica and be overtreated with prednisone than the younger patient with FM. The symptoms and signs differentiating FM from PMR are listed in Table 15.3 [22].

The management of sleep disturbances due to fibromyalgia in the elderly

The elderly patient is particularly prone to the complications associated with polypharmacy. The many disturbing symptoms of FMS are an invitation for multiple drug prescriptions, which can be disastrous in the elderly patient.

The sleep disturbance should be investigated to ascertain whether periodic limb movement syndrome, sleep apnea, bruxism or acid reflux disease is present. Psychiatric and medical co-morbidities such as depression, dementia, hypothyroidism or inflammatory arthritis interfering with sleep should also be considered. Improved quality of sleep in FM has been correlated with decreased musculoskeletal pain, better quality of life, and less fatigue.

Sleep hygiene

Sleep hygiene is important to discuss with every patient with FM [31]. Patients must ensure that their sleep environment is dark, quiet, and that the bed and mattress are conducive to a good night's rest. Taking a hot shower before sleeping and creating a restful environment during the hour before going to sleep also helps. It is important to eliminate excessive alcohol and all caffeine if possible. If a patient gets up in the middle of the night and is not able to sleep, it is better to read for about an hour and return to bed and then wake up at the same time as usual.

Medication

Since few studies have evaluated sleep therapies in FM and particularly elderly patients with FM, the use of medications to improve sleep must be approached with caution. Elderly patients are more prone to excessive daytime sedation and risk of falling due to dizziness or drowsiness in the morning.

1. Medication should only be used in patients who have failed implementation of sleep hygiene regimens particularly due to the risk of falls in the elderly population.
2. If there are other medical or psychiatric considerations that are suspected, then these should be confirmed and appropriate treatment

Table 15.3. Comparison of polymyalgia rheumatica (PMR) and fibromyalgia (FM)

Characteristic	PMR	FM
Age	>50 years	Any age
Gender ratio F:M	2:1	8–9:1
Distribution of pain	Shoulder and hip girdle	Diffuse
Axial skeletal pain	Present but not anterior chest pain	Present
Duration of pain needed for classification	>1 month	>3 months
Sleep disturbance	Variable	Present
Fever	Low grade	Absent
Fatigue	Present	Present
Morning stiffness and gelling	Present	Present
Synovitis	May be present	Absent
Laboratory abnormalities	Elevated ESR, mild anemia, thrombocytosis	None
Response to steroids	Excellent	Absent
Response to tricyclics	None	Good

instituted. Psychiatric conditions such as depression, anxiety or agitation should be treated with the lowest dose of selective serotonin antagonist, short-attacking anxiolytic such as lorazepam at night or the lowest dose of antipsychotic agent such as haloperidol. Medical conditions such as obstructive sleep apnea or polymyalgia rheumatica need to be treated with continuous positive airway pressure therapy or anti-inflammatory therapy, respectively.

3. If medication is to be used for the management of insomnia in the elderly patient with FM, a medication with a shorter half-life such as lorazepam should be used. Some medications that have a short half-life such as zolpidem may cause symptoms such as hallucinations and sleepwalking and may not be suitable for the elderly [32]. Other options in a few selected patients include tricyclic antidepressants, which promote sleep with or without muscle relaxation; these include cyclobenzaprine, trazodone, amitryptiline or doxepin in low doses given 1–2 hours before going to bed [33, 34, 35].
4. Selected patients may benefit from over-the-counter supplements such as melatonin or 5-hydroxytryptophan [36, 37].
5. Non-medicinal methods of promoting stress reduction and encouraging restful sleep include hypnotherapy, acupuncture, and electroacupuncture, meditation, and behavioral therapy, and supervised exercise may work in some patients [38, 39, 40, 41, 42].
6. A recent Internet survey of 2596 patients with self-reported FM revealed that about 30–40% voiced ongoing use of either cyclobenzeprine, amitryptiline, zolpidem or a benzodiazepine for their insomnia due to FM [43].

Summary

Fibromyalgia is a pain amplification syndrome produced by persistent afferent sensory stimulation and manifested as a central sensitization syndrome. It is not a disease, but is present in a variety of medical and behavioral conditions and is very prevalent in the elderly population. FM is modified by hormonal, cytokine, neurotransmitter, and autonomic influences. The overwhelming majority with FM have sleep disorders, with the alpha-delta abnormality being the principal pathology. Managing sleep pathology in FM appropriately ameliorates the symptoms and signs of the syndrome more than almost any other intervention.

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Part 3
Chapter
16

Sleep disorders in the elderly

Sleep and pain management in the elderly

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Introduction

The prevalence of pain tends to increase with each decade of life. Many health conditions associated with aging are chronic and painful (e.g. osteoarthritis, rheumatoid arthritis, joint and bone disorders, neurological disorders). The sequelae of living with persistent pain often encompass physical deconditioning, depression, disability, social isolation, polypharmacy, increased healthcare utilization, poor sleep, and fatigue. Sleep disturbance is particularly salient because the association between sleep and pain can be reciprocal; while pain itself (along with typical pain-related medications and altered lifestyle) certainly disturbs sleep, recent evidence suggests sleep loss may lower pain threshold. Thus, pain can diminish sleep and sleep loss can exacerbate pain in a vicious cycle.

As detailed below, epidemiological evidence indicates a very substantial proportion of older adults suffer from persistent pain. Despite its prevalence and broad-scale implications for health and quality of life, pain has been inadequately studied, evaluated, and treated in seniors. While our armamentarium of effective pharmacological and non-pharmacological treatments to manage pain and insomnia is sizeable, these measures unfortunately have been under-utilized for older adults (especially seniors with sensory or cognitive impairment) because of under-reporting, inadequate screening, concerns over adverse events, and other barriers.

Pain management is increasingly recognized as a contributor to therapeutic effectiveness across a broad range of medical conditions in terms of improved outcomes and patient satisfaction. Within the past decade, interdisciplinary pain and geriatric societies have collaborated to produce clinical practice guidelines for assessment[1] and treatment of pain in older adults [2, 3, 4, 5]. Healthcare initiatives such as guidelines from the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) have called for an increased awareness of the impact of chronic pain and have recommended that physicians routinely assess and treat pain [6]. Many institutions have adopted the routine practice of monitoring pain as the "5th vital sign" [2, 6].

While few would dispute the ethical and clinical importance of relieving pain, the process can prove challenging. Clinical manifestations of persistent pain are commonly multifactorial. Evidence-based guidelines emphasize the need for thorough evaluation of the pain–sleep–mood symptom constellation as well as functional status, co-morbid illness, and medications. Multimodal therapies are often needed to manage pain. Although there are a limited number of outcome trials in older adults, available evidence suggests elderly patients with persistent pain benefit from available therapies for both insomnia and pain management. This chapter describes the nature of pain, epidemiology of non-malignant pain and co-morbid sleep problems in older adults, the proposed bidirectional relationship between sleep and pain, and recommendations for evaluation and management of persistent, non-malignant pain drawn from evidence-based guidelines enhanced with emphasis on sleep.

Nature of pain

Pain has been aptly defined by the International Association for the Study of Pain (IASP) as "an unpleasant sensory and emotional experience arising from actual or potential tissue damage or described in terms of such damage" [7]. Neuroanatomical pathways of nociception are known to project to the sensory and associative cortex, making emotional arousal an inevitable consequence of pain perception. The IASP definition underscores both emotional and sensory elements of pain and helps to account for substantial individual differences in pain experience. There is no objective "pain thermometer" or readily observable biological markers to quantify pain. The experience of pain is subjective, highly individualized, and frequently does

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not correlate with the objective degree of injury or disease. Myriad factors may influence pain perception (e.g. biological aging, prior experience, attitudes, beliefs, expectations, memory, presence and response of significant others, fear, cultural norms). For example, consider a 25-year-old student, a 50-year-old laborer, and a 75-year-old retiree who experience a similar back injury. Age-related differences in physical, psychological, and social variables are likely to lead to very different pain experiences on the part of the individual, as well as differing responses from significant others and healthcare providers. Thus, pain is often conceptualized using a biopsychosocial model [8] recognizing that nociceptive input is modulated by individual central nervous system activity (i.e. arousal), psychological factors (e.g. depression, cognitive beliefs), environmental consequences (e.g. reinforcement, stressors), and conditioning or learning history [9, 10].

Acute pain often is associated with an identifiable injury or trauma, generally short in duration and remits as the disease process or injury heals. Acute pain serves an essential biological function, alerting the individual of threat and motivating behaviors to withdraw or minimize harm. With the progression from acute to chronic, pain outlasts its biological utility for self-preservation. Although there is no diagnostic time frame, pain often is adjudged "chronic" when it persists for 6 months or when it persists beyond anticipated healing time. Chronic pain may be perpetuated by a host of maladaptive responses resulting in further loss of physical function, depression, catastrophizing, and helplessness (Figure 16.1) [11]. When pain is persistent or associated with emotional, cognitive, and behavioral impairment, a comprehensive pain management plan that addresses biopsychosocial factors is necessary [12]. Notably, the term "chronic pain" is considered to have become a label entrenched with negative stereotypes (e.g. futility in treatment, malingering, drug-seeking behavior). Thus, many professionals prefer the term "persistent pain," which may foster a more positive attitude among patients and providers.

Epidemiology of pain and sleep complaints

Pain is associated with numerous acute and chronic medical conditions, and older individuals often experience multiple sources of pain. Disorders characterized by persistent pain that commonly afflict the elderly are included in Table 16.1 and listed within four major categories. Helme and Gibson [13] reviewed the epidemiological literature regarding pain in the geriatric population including prevalence, duration, and site of pain, and strengths and weaknesses of studies. Eleven community-based studies published from 1984 to 1999 and including data from individuals from 55 to >85 years of age were reviewed (sample sizes ranged from 148 to 3673 participants). Findings of prevalence varied widely, probably due in part to varying research methods. Among individuals ≥65 years of age, 25% to 88% of respondents reported pain. Pain associated with degenerative joint disease was estimated to account for more than two-thirds of pain complaints among older adults. The prevalence of joint pain more than doubled in adults over 65 years of age when compared to younger samples. Overall, pain increased with age at least through the seventh decade of life with an apparent subsequent decline (although the authors acknowledged their poorest response rate was from the eldest age group which may have under-represented the pain prevalence estimate among this age group). Temporary pain conditions tended to be similar across ages, while persistent pain increased with age. Generally, the prevalence of head, abdominal, and chest pain was reduced among older people, whereas musculoskeletal joint pain increased by age at least until 80 years of age.

Persistent pain is more prevalent among older adults in nursing homes and long-term care facilities than community residents. The review by Fox and colleagues [14] identified six prevalence studies addressing pain among elders living in institutional settings. Published between 1986 and 1995, these studies reported data from samples ranging in size from 92 to 758 individuals and yielded prevalence rates for pain of 49% to 83% (self-report or chart review). Like community-based studies, the predominant painful conditions (reported in four studies) were musculoskeletal in nature.

Prevalence of sleep complaints with pain

Pain consistently is associated with sleep complaints in community-based studies considering adults across the age span [15, 16, 17] and particularly among seniors [18, 19, 20, 21, 22]. The 2003 National Sleep Foundation "Sleep in America" Survey examined the relationship between sleep, pain, and major medical illnesses [18, 19]. The survey included telephone interviews

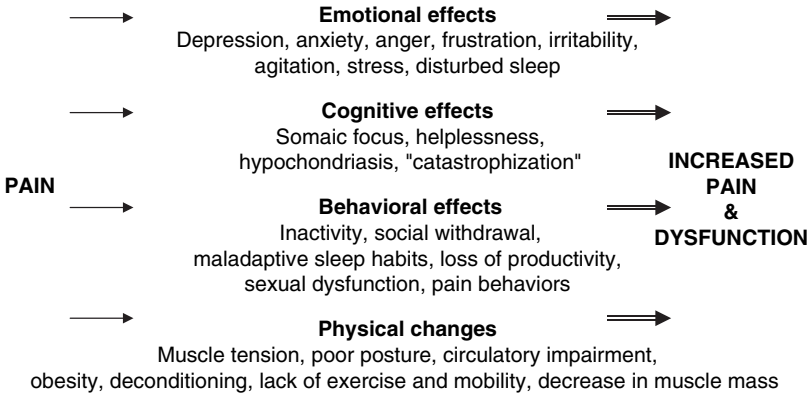

Figure 16.1. Emotional, cognitive, behavioral, and physiological effects manifested concurrently with increased pain and dysfunction. (Adapted from reference [11].)

of 1506 community-dwelling adults (55–84 years) randomly sampled from USA census data [19]. Four out of five participants reported at least one major medical condition, with the most common being hypertension (47%), arthritis (46%), heart disease (18%), diabetes (16%), depression (16%), and cancer (14%). One in four individuals (age 65–84 years) reported a total of four major medical conditions.

Table 16.1. Categories and examples of persistent pain outlined by the American Geriatric Society*

Nociceptive pain
Arthropathies (e.g. rheumatoid arthritis, osteoarthritis, gout, post-traumatic arthropathies, mechanical neck and back syndromes)
Myalgia (e.g. myofascial pain syndromes)
Skin and mucosal ulcerations
Non-articular inflammatory disorders (e.g. polymyalgia rheumatica)
Ischemic disorders
Visceral pain (pain of internal organs and viscera)
Neuropathic pain
Post-herpetic neuralgia
Trigeminal neuralgia
Painful diabetic polyneuropathy
Post-stroke pain (central pain)
Post-amputation pain
Myelopathic or radiculopathic pain (e.g. spinal stenosis, arachnoiditis, root sleeve fibrosis)
Atypical facial pain
Causalgia-like syndromes (complex regional pain syndromes)
Mixed or unspecific pain
Chronic recurrent headaches (e.g. tension headaches, migraine headaches)
Vasculopathic pain syndromes (e.g. painful vasculitis)
Psychologically related pain syndromes
Somatization disorders
Conversion disorders

*Pain types and contributing factors are not mutually exclusive. Patients frequently do have more than one type of pain, as well as overlapping contributing factors.

From Reference [2].

Chronic bodily pain, depression, heart disease, and memory problems were associated with symptoms of insomnia. Daily bodily pain was reported by 35% of respondents, and these individuals were at significantly greater risk than those without pain for insomnia symptoms (i.e. difficulty falling asleep, difficulty staying asleep, waking too early, and waking unrefreshed), sleeping <6 hours per night, daytime sleepiness, snoring, and unpleasant feeling in the legs (all $P < 0.05$), as well as napping (4 to 7 days per week) [18]. Individuals with one or more major medical condition were at greater risk for sleep problems than individuals with no major medical conditions suggesting pain and medical illness rather than aging per se accounted for much of the sleep disturbance observed among the elderly. These findings are highly consistent with other recent studies [23, 24].

Bidirectionality of pain and sleep

The relationship between pain and disturbed sleep initially appears straightforward and intuitive – pain provokes emotional arousal and arousal interferes with the ability to initiate and maintain sleep. However, the relationship between sleep and pain is considerably more complex and is not unidirectional. Instead, the relationship appears reciprocal in nature, where pain disturbs sleep and sleep loss impacts threshold or perception of pain. There is experimental and clinical evidence supporting the bidirectionality of sleep and pain. For example, a classic and often-cited study conducted three decades ago experimentally manipulated slow wave sleep versus rapid eye movement in healthy young adults [25]; the group for whom slow wave sleep was compromised exhibited next day muscle tenderness, musculoskeletal symptoms, fatigue, and in some cases appetite changes. This sleep disturbance (i.e. alpha-delta sleep) and symptom constellation has been closely associated with fibromyalgia and chronic fatigue syndrome (see chapters in this volume). Subsequent experimental studies using sleep restriction [26] or selective slow wave sleep deprivation [27, 28] have lent some degree of support to the adverse impact of sleep manipulation or deprivation on pain sensitivity. A few clinical studies have correlated severity of sleep disturbance with next day pain. For example, among 50 women with fibromyalgia (mean age = 44 ± 8.2 years) using an electronic daily pain/sleep diary for 30 days, Affleck and colleagues [29] demonstrated significant within-subject relationships in which poor sleep was followed by greater pain ratings. Research and commentary addressing the bidirectionality of sleep and pain is reviewed extensively elsewhere [30, 31, 32]. To our knowledge, this relationship has not been studied experimentally or clinically in older adults.

Biopsychosocial factors in pain and sleep

Pain has been associated with increased risk for depression [20, 33, 34, 35], activity limitation or disability [22, 35, 36, 37], polypharmacy [20, 37], poorer quality of life [22, 38, 39, 40], and increased healthcare utilization [22].

Depression

A high percentage of individuals with chronic pain have co-existing depression (across the age range). Among elderly populations, 1% to 3% have major depression and 8% to 16% have significant depressive symptoms with physical illness, sleep disturbance, disability, bereavement, and female gender recognized to increase risk [41, 42]. In 2004, the World Health Organization [43] examined data from primary care centers worldwide and found 22% of patients suffer from persistent pain. Pain patients were four-fold more likely to have co-morbid depressive disorder than pain-free primary care patients [43]. The findings also showed that the more diffuse the pain complaints, the greater the risk of depression and the greater adverse impact on the quality of life. Notably, depression in older adults may be characterized by impairment of cognition, a syndrome sometimes referred to as pseudodementia.

Suicide

Individuals with chronic pain are at increased risk for suicidal ideation. Smith and Haythornthwaite [32] examined pain severity, sleep, and depression among 51 individuals (ages 18–70 years; mean = 44 ± 11) with non-cancer pain ≥6 months' duration recruited from the community. Twelve were classified passive "suicidal ideators" (i.e. "I have thoughts of killing myself but would not carry them out") and compared to "non-suicidal ideators" (N = 39). None reported suicidal intent. Groups did not differ with respect to age or other demographic variables. Individuals with chronic pain who reported severe and frequent initial insomnia (with concomitant sleep-related daytime

dysfunction) and high pain intensity were significantly more likely to acknowledge suicidal ideation. Notably, sleep onset disturbance and high pain intensity were more robust discriminators of suicidal ideation than increased depression, affective distress, or pain-related interference in daily activities.

Disability

Pain is associated with varying degrees of disability and may ultimately determine an older individual's ability to live independently. Scudds and Robertson [36] examined pain and disability among 885 community-dwelling seniors (mean age = 76 ± 5.83 years). The most common pain complaint was musculoskeletal pain (N = 644). Level of self-reported disability was related to greater pain severity, pain frequency, pain medications, number of pain locations, number of chronic medical conditions, sleep disturbance, and increased age.

Cognitive function

Cognitive function may be impaired in individuals with persistent pain. McCracken and Iverson [44] assessed cognitive function in 275 consecutive adult pain clinic patients (age = 47 ± 13.8 years). The patients' pain was longstanding (mean chronicity = 64 ± 80.3 months), and low back pain was the predominant complaint (55% of patients). Patients with head trauma and stroke were excluded. The most common cognitive symptoms included forgetfulness (23%), minor accidents (23%), difficulty finishing tasks (21%), decreased attention (19%), difficulty concentrating (17%), and making mistakes (15%). Depression accounted for 29% of the variance in cognitive complaints. Cognitive complaints also were significantly correlated with pain severity (r = 0.24), pain-related anxiety (r = 0.46), sleep disruption (r = 0.17), use of antidepressant medications (r = 0.35), and use of narcotic medications (r = 0.16). Cognitive complaints were not related to age (r = 0.04).

Barriers

There are multiple barriers to effective pain and sleep management. Concerning pain, common barriers exist for all individuals such as inadequate training of healthcare professionals in pain assessment, limited practical assessment tools, reluctance to prescribe opiates, social stigma, fear of addiction, fear of being perceived as drug-seeking, cost concerns, etc. Some barriers are unique or disproportionate to seniors [45, 46]. Relative to younger patients with persistent pain, the elderly are at greater risk for sensory and cognitive impairment, which makes communication more difficult. Common pain conditions in seniors that follow a subtle onset and gradual progression are less likely to raise concern from significant others and providers. Myths are prevalent that pain is a natural and inevitable aspect of aging, and stoicism is often inappropriately expected of mature individuals.

A comprehensive study of barriers to pain management was recently conducted [47]. Elderly residents from 12 rural and urban nursing homes in Colorado were randomly selected, and self-report and behavioral indicators of pain were collected. A total of 2033 residents completed pain interviews and/or were observed for pain behaviors by trained research staff. All residents were asked if they had pain (or a synonym for pain) at the time of interview or within the past 24 hours and medical records were reviewed for documentation of pain and its treatment. Residents experiencing pain were interviewed and asked to provide up to three reasons for not requesting pain medication. Sixty percent of individuals in pain or with pain in the past 24 hours did not request medication for that pain. The most commonly stated reasons for not seeking treatment were medication concerns and stoicism. Concerns about staff reactions to a request or perception that staff members were too busy also were commonly reported. Individuals not reporting pain were more likely to have both continuous and intermittent pain problems compared to those with solely intermittent pain or solely continuous pain. The older residents were less likely than younger to report pain (80 ± 12 versus 78 ± 13 years). Also, residents of rural (compared to urban) nursing homes and white (compared to non-white) ethnicities were less likely to report pain.

Barriers to sleep management also have been identified. In a recent review [48], a number of factors were cited as contributing to poor recognition, diagnosis, and treatment of insomnia in the primary care setting, including inadequate knowledge base on the part of healthcare providers, office visit time constraints, under-reporting by patients, misperceptions regarding the safety and efficacy of pharmacological treatments, lack of awareness or access to non-pharmacological treatments, and lack of evidence for functional outcomes (e.g. long-term efficacy, impact on co-morbid conditions).

Pain management in older adults

Guidelines based on available evidence, supplemented with expert consensus, provide a framework for assessment and treatment of persistent pain in older adults [2, 3, 4, 5]. The seminal work in this area, published by the American Geriatrics Society (AGS) Panel on Persistent Pain in Older Persons in 1998 [3] and updated in 2002 [2], yielded key recommendations concerning geriatric pain management (Table 16.2). Building upon this work, an international expert consensus on pain assessment in older persons was published in 2007 with evidence supporting the validity of pain intensity assessment scales for older persons, including validated behavioral scales to use with cognitively impaired patients (endorsed by the IASP Special Interest Group on Pain in Older Adults) [1].

The AGS Panel guideline [2] acknowledges the importance of classifying persistent pain in pathophysiological terms. The guideline offers four basic pain categories (Table 16.1) that encompass most relevant pain-related syndromes and have implications for treatment. The guideline does not address disease-specific treatments but instead offers general recommendations for pain management based on categories of pathophysiology. Nociceptive pain may be either visceral or somatic and is due to stimulation of pain receptors, and among elderly patients may be the result of inflammation or musculoskeletal or ischemic disorders; nociceptive pain mechanisms generally respond to common analgesics and non-pharmacological treatments. Neuropathic pain involves the central or peripheral nervous system, which do not respond as predictably to conventional analgesics as nociceptive pain, but may respond to unconventional analgesic or adjuvant treatments such as tricyclic

Table 16.2. Summary of key recommendations from the American Geriatrics Society Panel on Persistent Pain in Older Persons*

■ The key to effective treatment of persistent pain lies in comprehensive assessment. All older persons should be screened for persistent pain on initial evaluation, on admission to any health care service, and periodically thereafter [II,B]. Any persistent pain that has an impact on physical function, psychological function, or quality of life should be considered a significant problem [II,A]
■ The verbally administered zero to ten scale is a good first choice for assessment of pain intensity; however, other scales such as word descriptor scales, faces scales, or pain thermometers may be more appropriate for some patients [II,A]
■ For those with moderate to severe cognitive impairment, assessment of behaviors and family or caregiver's observations are essential [II,A]
■ Acetaminophen should be the first drug to consider in the treatment of mild to moderate pain of musculoskeletal origin [I,B]
■ Traditional (i.e. non-selective) non-steroidal anti-inflammatory drugs (NSAIDs) should be avoided in those who require long-term daily analgesic therapy [I,A]
■ Opioid analgesic drugs may help relieve moderate to severe pain, especially nociceptive pain [I,A]. Opiates are effective, associated with a low potential for addiction, and overall may have fewer long-term risks than other analgesic drug regimens in older persons with persistent pain. As with all medication, careful monitoring for the development of adverse side effects is important
■ Non-opioid analgesic medications may be appropriate for some patients with neuropathic pain and some other persistent pain conditions [I,A]
■ An individualized program of physical activity should be designed to improve flexibility, strength, and endurance, and should be maintained indefinitely [I,A]
■ Patient and caregiver education is an essential component in the management of persistent pain [I,A]
■ Formal cognitive-behavioral therapies are helpful for many older adults with persistent pain [I,A]
■ Health-care facilities that care for older patients should routinely conduct quality assurance and quality improvement activities to enhance pain management [II,B]

*Quality and strength of evidence ratings follow each recommendation in brackets. **Quality of evidence**: Level I – evidence from at least one properly randomized, controlled trial; Level II – evidence from at least one well-designed clinical trial without randomization, from cohort or case controlled analytical studies, from multiple time-series studies, or from dramatic results in uncontrolled experiments; Level III: evidence from respected authorities, based on clinical experience, descriptive studies, or reports of expert committees. **Strength of evidence**: A – good evidence to support the use of a recommendation and clinicians should do this all the time; B – moderate evidence to support the use of a recommendation and clinicians should do this most of the time. None of the evidence rated C, D, or E are listed among Key Recommendations.

From Reference [2].

antidepressants, anticonvulsants, and antiarrhythmic drugs. Pain of mixed or unspecified origins respond less predictably and may require trials of combined approaches. Non-specific pain related to psychological factors would not call for traditional analgesic medications and may warrant specific psychiatric treatments. Guideline recommendations are briefly summarized here (Table 16.2), but the guidelines should be consulted for the complete recommendations and quality and strength of evidence ratings, as well as specific medication and regimen recommendations [2].

Assessment of persistent pain

Screening of all older adults for pain on initial presentation to any healthcare service or professional is advised. A verbally administered 0–10 numeric scale ("On a scale of zero to ten, with zero meaning no pain and ten meaning the worst pain possible, how much pain do you have right now?") or visual analog scale is a good first choice for measuring pain intensity. Other verbal descriptor scales, pain thermometers, and faces pain scales are available for individuals with cognitive impairment [1, 2]. Persistent pain impacting physical or psychosocial function or quality of life should be regarded as significant and warranting a comprehensive pain assessment to elucidate remediable factors. History should include pain characteristics and development, past treatments, activities of daily living, and attitudes or beliefs about pain. Physical examination as well as pertinent laboratory, psychological, social, and cognitive assessment should be completed. Patients with dementia or verbal limitations should be observed for evidence of pain (Table 16.3) and history taken from care-givers. Risks and benefits of assessment and treatment options should be determined in collaboration with patients and family. Pain should be reassessed at regular intervals using quantitative pain assessment questionnaires or diaries, and treatment plans revised accordingly.

Pharmacological treatment

Pharmacotherapy remains the primary treatment to control pain and the AGS Panel guideline [2] has reiterated that there is no role for placebos in the assessment or management of pain in older patients. The least toxic and least invasive treatments should be considered preferentially. Acetaminophen should be considered as first line treatment in mild to moderate nociceptive pain conditions. Opioid analgesic medications are indicated to relieve moderate to severe pain (especially nociceptive pain). Non-steriodal anti-inflammatory drugs (NSAIDs) should be avoided in patients who require long-term daily analgesic therapy. Because of lower incidence of gastrointestinal bleeding, cyclo-oxygenase-2 (COX-2) inhibitors were recognized as a safer alternative to NSAIDs, but a recent association with heart disease has decreased acceptance. The guideline provides recommendations for dosing regimen, titration, side-effect management, breakthrough pain, and follow-up. Evidence supports use of adjuvant medications including anticonvulsants and antidepressants in managing neuropathic pain. In most cases, use of these medications is off-label. Tricyclic antidepressants such as amitriptyline, nortriptyline, and desipramine have demonstrated duel benefits to pain and sleep or depression, but are associated with significant and often unacceptable adverse effects such as cardiotoxicity, hypotension, sedation, and confusion. Gabapentin and other anticonvulsant drugs with relatively benign side-effect profiles are often preferred. All such pain-modulating drugs require careful titration, monitoring, and regular follow-up to assess effectiveness and side effect and thus must be considered on a case-by-case basis. Recommended clinical endpoints include decreased pain, increased function, and improvements in mood and sleep.

Non-pharmacological treatment

Non-pharmacological treatments (i.e. physical and psychological) also were addressed by the AGS Panel guideline [2]. A physical activity program that is individualized to abilities and goals is recommended for all patients with persistent pain. Patient education programs should address components of pain management such as self-help techniques (e.g. relaxation, distraction), causes of pain, treatment options, and appropriate analgesic use and education should be reinforced in every patient encounter. Use of local resources should be encouraged, such as self-help groups and disease-specific organizations. Formal cognitive-behavioral therapies are recognized as effective alone or in combination with pharmacotherapy and are recommended. Therapy should be carried out by professionals in a structured format in programs using patient education, a clear rationale for therapy, cognitive and behavioral coping skills training, methods to generalize coping skills to daily living, and

Table 16.3. Common pain behaviors in cognitively impaired elderly persons

Facial expressions
Slight frown; sad, frightened face
Grimacing, wrinkled forehead, closed or tightened eyes
Any distorted expression
Rapid blinking
Verbalizations, vocalizations
Sighing, moaning, groaning
Grunting, chanting, calling out
Noisy breathing
Asking for help
Verbally abusive
Body movements
Rigid, tense body posture, guarding
Fidgeting
Increased pacing, rocking
Restricted movement
Gait or mobility changes
Changes in interpersonal interactions
Aggressive, combative, resisting care
Decreased social interactions
Socially inappropriate interactions
Withdrawn
Changes in activity patterns or routines
Refusing food, appetite change
Increase in rest periods
Sleep, rest pattern changes
Sudden cessation of common routines
Increased wandering
Mental status changes
Crying or tears
Increased confusion
Irritability or distress

Note: some patients demonstrate little or no specific behavior associated with severe pain.

From reference [2].

relapse prevention. Significant others may be involved in therapies. Other modalities may offer temporary relief and can be used as adjunctive measures (e.g. heat, cold, massage, acupuncture, transcutaneous electrical nerve stimulation).

Sleep management in older adults with persistent pain

The above recommendations call for screening of *all* elderly patients for pain, based on risk and implications for health and quality of life. Based on prevalence of sleep disturbance among pain sufferers and potential for pain to worsen in the context of poor sleep, it may be equally important that all patients with persistent pain be screened for sleep disturbance. Sleep management for those patients who also have persistent pain involves several goals (Table 16.4).

Diagnose and treat primary sleep disorders

Sleep management begins with a thorough assessment of sleep with a sleep history and physical examination. As evident throughout this book, a wide range of sleep disorders are prevalent among seniors independent of pain and multiple sleep abnormalities may co-exist. Assessment and differential diagnosis of sleep disorders in the elderly is detailed elsewhere in this volume. The sleep history can provide pertinent information that often is not adequately addressed in the standard pain history. Of interest are the timing of sleep and wake, habits (e.g. reading or television in bed, "hitting the snooze"), pre-sleep routine, sleep environment (e.g. light, noise, television or other stimulation), a description of the sleep period itself, daytime alertness versus sleepiness, laying in bed for long periods awake or "resting," napping, drug effects (e.g. sedating or alerting medications, alcohol, caffeine, nicotine), and any special measures to promote sleep or wake. Useful information may be obtained not only from the patient, but also from the bed partner or other observer when feasible.

Simple screening questions can direct the sleep history to identify patients "at risk" for sleep disorders. Inquiring about the *Restorative* nature of the patient's sleep, *Excessive* daytime sleepiness, tiredness or fatigue, the presence of habitual *Snoring*, and whether the *Total* sleep time is sufficient, can be revealing. The mnemonic *REST* can help the clinician remember these four key questions in the screening history. Patients suspected of sleep-related breathing disorders, movement disorders, and other parasomnias warrant polysomnographic evaluation and appropriate treatments. The most common sleep complaints related to pain included difficulty initiating sleep, nocturnal awakenings,

Table 16.4. Goals for sleep management in older adults with persistent pain

I. Diagnose and treat primary sleep disorders
■ Sleep history
■ Review medications for contributory sedating or alerting effects
■ Establish provisional diagnosis of sleep disorder, such as:
· Sleep-related breathing disorders
· Circadian rhythm disorders
· Movement disorders
· Parasomnias such as REM sleep behavior disorder, nightmares, etc.
· Insomnia (most common sleep complaint with persistent pain)
■ Consult sleep specialist or refer for polysomnography as needed
II. Determine the adequacy of pain management in the context of best practice guideline [2]
■ Pain history
· Nociceptive, neuropathic, mixed/unspecified, other
· Intermittent versus continuous
· Severity (quantitative ratings, questionnaires, significant other, behavioral observation)
· Functional impairment
■ Determine relationship between pain and sleep complaint
· Pain-related behaviors, cognitions and emotions contributing to maladaptive sleep habits (e.g. daytime resting, laying in bed, napping, or inactivity reducing nocturnal sleep drive; pain awakenings; worry, fear or rumination at night; emotional distress)
· Impact of sleep on pain level, coping, functional abilities
■ Consider adequacy of current pain treatments
· Pharmacological treatment (non-opiate analgesic, opiate, adjuvant medications), dosing schedule (e.g. intermittent short-acting for flares, long-acting time-dependent for continuous pain), route of administration, side-effect management and compliance are appropriate
· Non-pharmacological treatments are utilized to reduce pain and maximize function, such as exercise regimen, proper body mechanics, pain-reducing modalities (e.g. heat, cold, physical therapy, massage, distraction), and cognitive-behavioral therapies (e.g. relaxation training, meditation, stress management, cognitive therapy)
■ Pain diary
· Ongoing subjective, quantitative assessment of pain by the patient enables both patients and providers to determine effectiveness of treatments (e.g. sleep, mood), fosters patient's self-management skills, and enhances self-efficacy
III. Identify and treat psychiatric co-morbidities
■ Mental status examination
■ Assess psychiatric symptoms and severity
· Depression
· Anxiety disorders
· Somatization disorders
· Substance abuse
■ Assess suicidal ideation, intent, plan (elevated risk with chronic pain and depression)
■ Treatment options as indicated
· Pharmacological treatments should take into account the constellation of pain, sleep, and mood symptoms. Antidepressants with alerting versus sedating properties, anxiolytic and anticonvulsant medications may be considered as dual purpose medications
· Psychological treatments such as cognitive-behavioral therapy for depression and anxiety may be used instead of or in combination with pharmacological treatment
IV. Identify and treat co-morbid insomnia

Table 16.4. (*cont.*)

■ Sleep education
· Age-related changes in sleep, sleep drive, circadian rhythms
· Impact of pain, pain-related lifestyle changes, cognitive reactions, and distress
■ Sleep hygiene (*general advice for all with persistent pain*)
· Relaxing pre-sleep routine
· Consistent bed and wake times (usually no more than 7–8 hours in bed)
· Sleep environment conducive to sleep (dark, quiet, comfortable)
· Avoid watching television and other alerting activities in bed
· Avoid or minimize daytime naps
· Maximize activity level and sunlight exposure during the day
· Avoid laying in bed "resting" from pain, worrying, or thinking about pain
■ Behavioral sleep therapy (*may be carried out in primary care setting by trained staff*)
· Stimulus control is indicated for difficulty falling asleep or staying asleep. Instructions include: (1) go to bed only when sleepy; (2) if unable to fall asleep in 10–20 minutes, leave the bedroom – return only when sleepy again; (3) use the bed and bedroom for sleep only; (4) set alarm and rise daily at a regular time; And (5) do not nap during the day
· Sleep restriction is indicated for individuals who spend excessive time spent in bed not sleeping or exhibit frequent awakenings. Instructions include: (1) use the sleep diary to determine "time in bed" and "actual sleep time;" (2) restrict "time in bed" to approximately the average number of hours of "actual sleep time" per night (prescribe specific bed/wake times); (3) as diary demonstrates actual sleep time is 85% of time in bed, increase by 15–30 minute increments; (4) keep a fixed wake time, regardless of the actual sleep duration; and (5) if sleeping <85% time in bed for 10 days, restrict time in bed further by 15–30 minute increments
■ Multicomponent cognitive-behavioral therapy (*referral to psychologist or sleep specialist*)
· Relaxation training for sleep promotion and pain management – to acquire skills to gain voluntary control over and reduce the state of hypervigilance that is incompatible with sleep or pain
· Cognitive therapy – to identify, challenge, and replace irrational beliefs and fears about sleep and sleep loss which provoke anxiety and perpetuate insomnia
■ Pharmacological interventions
· Hypnotic medication indicated for short-term, intermittent or extended use – zolpidem, zolpidem tartrate extended release, eszopiclone, and zaleplon
· Dual purpose medications for pain, depression and/or sleep include anticonvulsant medications (e.g. gabapentin, clonazepam, carbamazepine) [2] and antidepressant (e.g. desipramine, nortriptyline, mirtazapine) [2 ,11] medications
V. Evaluation and maintenance
■ Repeated assessment of pain as 5th vital sign on follow-up
■ Re-evaluate risk–benefit analysis of pain, psychiatric and sleep-promoting medications at regular intervals
■ Reinforce continued behavioral sleep and pain self-management skills

non-restorative sleep, and fatigue (often termed "secondary insomnia" or "co-morbid insomnia" and discussed below) [19].

Determine the adequacy of pain management in the context of best practice guidelines

Familiarity with the elements of a patient's pain history and severity (using validated pain questionnaires, prospective diary, or verbally administered rating scales) along with the sleep history will enable the clinician to assess the relative contribution of ongoing pain to the sleep complaint. Optimal pain management is an ongoing treatment objective and should be assessed on an ongoing basis. Treatable pain is often unreported or untreated in the elderly, and those cases warrant treatment with pharmacological and/or non-pharmacological pain strategies. At the same time, sleep disturbance such as co-morbid insomnia may become a severe and relatively independent problem over time and will not necessarily remit with pharmacological or

non-pharmacological pain management. Cognitive-behavioral therapies (e.g. relaxation training for pain, cognitive pain coping skills training, pain-related behavior therapy) are effective in the treatment of pain [49], but it has not necessarily been shown to improve co-morbid insomnia [50]. Thus, specific cognitive-behavioral techniques tailored to insomnia may be required.

Pain questionnaires

There exists a very wide variety of reliable and well-validated instruments designed for the assessment of pain. Fortunately, there is considerable research supporting the use of quite a number of these measures for use with elderly pain patients (see Hadjistavropoulos and colleagues [1], tables 11–13 for an in-depth listing and description). The approach to pain measurement necessarily depends upon the purpose of the assessment, pain etiology, the patient's cognitive capacity, the clinical setting, and other important considerations. Recognizing the limitations and time pressures inherent in a busy clinical practice setting, the authors of the Interdisciplinary Expert Consensus Statement on Assessment of Pain in Older Persons [1] have recommended a brief (10 minute) pain assessment strategy as being well suited for older patients who are cognitively intact. The recommended measures include the Brief Pain Inventory (BPI; pain intensity and location, interference with function, medication use, and perceived relief with intervention) [51] along with the Short Form McGill Pain Questionnaire (SF-MPQ; pain quality) [52]. These measures not only are well validated with a broad range of pain patient populations, but their combined scope is consistent with the biopsychosocial conceptualization of chronic pain.

Pain diary

A pain diary can prove a helpful tool for the measurement of pain severity and pain-related activity. Diaries can be especially helpful for examining factors that can exacerbate or improve pain status and pain-related activity. A particularly useful diary for the daily self-monitoring of pain in the elderly is available for download at the AGS website (http://www.healthinaging.org/public_education/pain/my_pain_diary.pdf). Items assessed on this diary include: pain location, pain intensity, activity at pain onset (or that exacerbates pain), medications and other interventions for pain, and more. A caveat to the use of daily diaries is that as cognitive functions deteriorate, patients often become less likely to self-report pain [1]. As diaries and other self-report measures rely on intact cognitive capacity and higher mental functions, the value of this approach is necessarily limited for cognitively impaired patients. Instead, observational assessment of pain behaviors such as those listed in Table 16.3 may be necessary to assess the pain level of the latter patients (e.g. apparent distress, grimacing, bracing, limping). Additional recommendations regarding the systematic observation of pain behaviors and the assessment of pain in patients with cognitive impairment are presented elsewhere [1].

Identify and treat psychiatric co-morbidities

A high percentage of individuals with persistent pain also experience psychiatric symptoms. Pain commonly is accompanied by emotional stress, frustration, increased irritability, anger, anxiety, agitation, depression, social withdrawal, financial distress, loss of libido, disturbed sleep patterns, diminished appetite, and/or weight loss [11]. Likewise, insomnia is co-morbid with a number of psychiatric disorders (e.g. depression, anxiety, somatization disorder, substance abuse). When such co-morbidities are present, concurrent psychiatric and substance abuse management may be needed.

At a minimum, a screen for the presence of significant psychological symptoms is needed. There are a variety of well-validated and efficient screening tools designed to facilitate psychological symptom assessment, and several of those instruments are highlighted here. Designed for use in medical settings, the PRIME-MD (Primary Care Evaluation of Mental Disorders) [53] is among the best validated instruments to assess the presence of a variety of co-morbid psychiatric disorders, and it is designed to screen for common psychiatric disorders based upon diagnostic criteria from the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders* [54]. The list of disorders screened by the PRIME-MD includes mood disorders (depression, bipolar), anxiety disorders (panic disorder, generalized anxiety disorder), eating disorders, alcohol abuse or dependence, and somatization disorders. The original PRIME-MD is a two-stage system that incorporates a 26-item self-administered symptom checklist and an additional clinician evaluation for patients who score positively on the questionnaire. Recognizing that the original PRIME-MD is somewhat time consuming to

administer (approximately 15 minutes), Spitzer and colleagues [55] also have released an entirely self-report version of the scale (Primary Care Evaluation of Mental Disorders – Patient Health Questionnaire; PRIME-MD PHQ), which is similarly well validated and comparable to the original version.

With the high prevalence of depression in the elderly as well as in patients with chronic pain, screening for depression is an essential part of pain management for the elderly chronic pain patient [56]. Objective self-report instruments for the assessment of depression that are psychometrically well validated and have been widely used with elderly populations include the Beck Depression Inventory (BDI; various versions) [57, 58, 59] and the Geriatric Depression Scale (GSD) [60]. The latter instrument may be preferred for patients older than 65 years owing to the relatively small number of somatic items (which can artificially inflate depression scores) in the GDS compared to the BDI [61].

Identify and treat co-morbid insomnia

While pain is a common initial precipitant of insomnia, pain itself may not be the most important perpetuating factor. Over time, the vicious cycle of pain and sleep disturbance may be perpetuated by a host of cognitive and behavioral factors. An individual's own responses to pain and sleep loss (e.g. resting in bed or napping to relieve pain, inactivity, caffeine for fatigue, medications, emotional arousal, worry) may ultimately lead to the development of conditioned insomnia. This process is consistent with the widely accepted cognitive-behavioral model using a classical conditioning paradigm to explain the development and persistence of chronic insomnia [62]. Reversing these maladaptive patterns through specific cognitive-behavioral sleep therapy has demonstrated efficacy for treatment of primary insomnia [63]. Compared to primary insomnia, relatively few randomized controlled trials have been reported for co-morbid insomnia or treatment of insomnia in later life. Available evidence supports the effectiveness of cognitive-behavioral therapy for insomnia with chronic pain [64, 65, 66] with preliminary evidence in the elderly [67]. Non-pharmacological interventions are considered essentially free of adverse effects and highly compatible with a pain management treatment model.

Sleep diaries or sleep/pain diaries can be highly informative for patients and clinicians in defining insomnia (e.g. sleep onset versus maintenance insomnia) as well as behavior patterns interfering with sleep (e.g. excessive amounts of time in bed not sleeping, resting, napping). Insomnia can be correlated with other factors such as pain level, when comprehensive diaries are used. Treatment outcomes can be assessed over time using the diary. The value of a systematic daily sleep diary with chronic pain patients has been demonstrated [68] and diary variables pertinent though not specific to this population are noted (e.g. number of hours slept, sleep onset latency, frequency of awakenings that resulted in trouble falling back to sleep, early morning awakening, quality of sleep, lack of restfulness, a comparison of the previous night's sleep compared to usual sleep).

Cognitive and behavioral sleep treatments are described extensively elsewhere in this book. Those techniques with demonstrated efficacy for chronic pain include sleep restriction and stimulus control [65, 66], relaxation training and stimulus control [67], and sleep hygiene, relaxation training and stimulus control [64]. Because of the apparent reciprocal relationship between sleep and pain, one may wonder if sleep restriction and other techniques that create a temporary state of sleep deprivation would exacerbate pain; while there is no evidence that sleep restriction exacerbates pain, one should be aware of the association and adjust treatment accordingly if a significant exacerbation of pain or other adverse events occur. In such cases, sleep compression (gradually reducing time in bed) rather than sleep restriction (abruptly curtailing time in bed to approximate actual nightly sleep time) may be considered [69]. Relaxation training (i.e. progressive relaxation training, EMG biofeedback, autogenic training) is commonly used in pain management and may be a particularly useful treatment for individuals with persistent pain as well as insomnia.

Treatment strategies should be calibrated to individual symptom patterns, severity, abilities, and preferences. Probably all persons with persistent pain would benefit from basic sleep hygiene strategies to prevent or reverse behavior patterns that are incompatible with sleep (e.g. maintain a regular sleep schedule, avoid napping, engage in exercise, appropriate substance use). Particularly, patients should be encouraged to avoid pairing the sleep environment with painful stimuli or distress (i.e. avoid resting or lying in bed awake while in pain). Specific behavioral insomnia treatments

(i.e. stimulus control, sleep restriction) can be delivered in the primary care setting by trained staff. Stimulus control is indicated for difficulty falling asleep or staying asleep, and is based on operant conditioning principles and reinforces associations between the "state of sleepiness" and the sleep environment. Sleep restriction is indicated for individuals who spend excessive time in bed not sleeping or exhibit frequent awakenings, and maximizes homeostatic "sleep drive" by restricting time in bed to approximately the actual sleep time. Patients requiring intensive interventions may be referred to a trained clinician or sleep specialist for cognitive or multicomponent cognitive-behavioral therapy, which is typically administered over the course of 6–8 weeks.

Pharmacological treatments for insomnia include benzodiazepine and non-benzodiazepine hypnotic, psychotropic, and over-the-counter medications – these medication options are discussed extensively in dedicated chapters within this book. Chronic use of hypnotics in the elderly remains controversial, and there is little compelling evidence to support the long-term use of hypnotic medication in elderly patients with persistent pain, although long-term intermittent or long-term use may be justified on a case-by-case basis. Dual purpose medications for sleep and analgesia may be considered when possible. Traditional antidepressants that have demonstrated dual effects on pain and sleep include tricyclic antidepressants such as amitriptyline, desipramine, and nortriptyline, but are often unacceptable due to side effects or contraindications [2, 70]. Mirtazapine, an atypical tetracyclic antidepressant, may be useful in the management of chronic pain with insomnia [11]. Compared to depression, neuropathic pain typically responds more quickly and to a lower dosage of antidepressants and pain relief occurs in both depressed and non-depressed patients, suggesting that the antinociceptive effects are independent of effects on mood [71]. Unlike the tricyclic antidepressants, the selective serotonin reuptake inhibitors (SSRIs) and serotonin/norepinephrine reuptake inhibitors (SNRIs) have limited analgesic effects [71]. Anticonvulsant medications (e.g. gabapentin, carbamazepine) that have shown therapeutic benefits and are indicated for a variety of neuropathic pain conditions with lower side-effect profiles than tricyclic antidepressants may provide a viable option in the management of pain and sleep [2, 11].

Evaluation and maintenance

Individuals with persistent pain require ongoing care with regular follow-up. Pain should be assessed at each follow-up visit, as the 5th vital sign. Likely, each follow-up would include an evaluation of the effectiveness of treatments and re-examination of the risk–benefit ratio for pain, psychiatric, and sleep-promoting medications. Follow-up visits also provide the opportunity to reassess and reinforce behavioral sleep and pain self-management skills.

Conclusion

Several milestones have been reached in pain recognition and treatment, but much remains to be accomplished in involving older adults in research and in translating the science into practice for seniors. Within the past decade, epidemiological evidence has demonstrated that pain is a significant and worldwide concern [33, 43]. The National Sleep Foundation and others have presented data defining the nature and magnitude of sleep problems in older adults with pain [18, 19]. It is now evident that approximately half of the population over the age of 65 years experience persistent pain, and a large proportion of those individuals also experience sleep problems, depression, cognitive impairment, disability, and poorer overall quality of life.

A seminal evidence-based practice guideline for pain management was published by the American Geriatrics Society Panel on Persistent Pain in Older Persons [2]. The Panel highlighted the need for screening all older patients for pain and provided recommendations for pharmacological and non-pharmacological pain treatments. Unfortunately, sleep management was beyond the scope of the guideline, and much remains to be accomplished in determining the optimal sleep treatment for elderly pain sufferers with sleep disorders (especially co-morbid insomnia). Although there is a large research literature evaluating pharmacological and non-pharmacological treatments for primary insomnia in middle-aged adults [63], there are precious few studies addressing co-morbid insomnia with pain in the elderly.

Optimal management strategies for the older adult with persistent pain include several goals such as identifying and treating primary sleep disorders, optimizing pain management, identification and treatment of psychiatric co-morbidities, and management of co-morbid insomnia with cognitive-behavioral

therapies and judicious pharmacotherapy. These recommendations represent a synthesis of available evidence and clinical judgment and highlight the great need for additional research. Efforts should be made to include older persons in randomized controlled trials of pharmacological and non-pharmacological treatments for insomnia and to conduct studies specifically targeting this population. It is hoped that future research will provide greater evidence to tailor clinical practice to the unique needs and abilities of older adults.

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Part 3
Chapter
17

Sleep disorders in the elderly

Effect of depression and anxiety on sleep in the elderly

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Introduction

Sleep disturbances and psychiatric disorders are intimately related. Sleep symptoms are common in many psychiatric disorders, and are included among the diagnostic criteria for several of these. A growing body of epidemiological data provides evidence that insomnia is a risk factor for the later development of psychiatric disorders, including mood, anxiety, and substance abuse disorders. Furthermore, the presence of severe insomnia is associated with worse treatment outcomes in depression, and its re-emergence may herald recurrences of mood disorders. On the other hand, psychiatric symptoms and disorders are among the strongest cross-sectional risk factors for insomnia, and many patients with sleep disorders present with co-morbid psychiatric conditions. Treatments for psychiatric disorders may have either positive or negative effects on sleep symptoms, and treatment of sleep disorders often leads to reduced psychiatric symptoms. Finally, brain systems that regulate mood states have input to brain systems that regulate sleep and wakefulness, supporting the close connection between psychological states and sleep. In this chapter, we will review in greater detail evidence regarding the connections between sleep and specific common psychiatric disorders, as well as potential treatment approaches. These associations are particularly relevant in older adults, given the high prevalence of both sleep and psychiatric disturbances that accompany aging.

Anxiety disorders

Generalized anxiety disorder

Definition and epidemiology

Generalized anxiety disorder (GAD) is characterized by an inability to control excessive worry or anxiety for at least 6 months [1]. This worry manifests as a range of symptoms, including restlessness, irritability, muscle tension, fatigue, and difficulty with concentration. Sleep disturbance, characterized by difficulty falling or staying asleep or restless unsatisfying sleep, is another symptom included in the diagnostic criteria (see Table 17.1). It is not surprising, then, that GAD sufferers may present with both subjective and objective sleep disturbances.

The lifetime prevalence of GAD is estimated at 5.7% [2]. In the elderly, one study found the prevalence of GAD to be 7.3% in a population aged 55–85 years [3]. One important risk factor for development of anxiety in the elderly is having a partner who becomes sick with a major illness [4].

Complicating the diagnostic picture, anxiety symptoms consistent with GAD often co-exist with a co-morbid depressive disorder. GAD most often follows a chronic, unremitting course, which is distinct from the more episodic pattern more commonly seen in elderly patients who have major depressive disorder [5]. Regardless of diagnostic classification, the impact of anxiety on the elderly individual remains significant, with a negative effect on functioning and well-being and an increased use of health services [6].

Effects on sleep

The co-occurrence of GAD and insomnia is well established [7, 8]. Subjectively, patients with GAD may complain of sleep disturbances that range from difficulty initiating and maintaining sleep to non-refreshing sleep quality. As is the case for individuals with chronic primary insomnia, bedtime for GAD patients may become fraught with concerns about falling asleep. These concerns in turn may become further magnified in a patient's mind until both psychological and physical tension pre-empts any further attempts at sleep. Daytime symptoms and poor functioning may then follow after a night of poor sleep quality. In some instances, therefore, other components of GAD, such as fatigue, difficulty with concentration, and irritability, may be seen as a secondary effect of this sleep disturbance. However, the usual distinction between

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Table 17.1. DSM-IV-TR criteria for generalized anxiety disorder

A. Excessive anxiety and worry (apprehensive expectation), occurring more days than not for at least 6 months, about a number of events or activities (such as work or school performance)
B. The person finds it difficult to control the worry
C. The anxiety and worry are associated with three (or more) of the following six symptoms (with at least some symptoms present for more days than not for the past 6 months):
(1) Restlessness or feeling keyed up or on edge
(2) Being easily fatigued
(3) Difficulty concentrating or mind going blank
(4) Irritability
(5) Muscle tension
(6) Sleep disturbance (difficulty falling or staying asleep, or restless unsatisfying sleep)
D. The focus of anxiety and worry is not confined to features of an axis I disorder, e.g. the anxiety or worry is not about having a panic attack, being embarrassed in public, being contaminated, being away from home or close relatives, gaining weight, having multiple physical complaints, or having a serious illness, and the anxiety and worry do not occur exclusively during post-traumatic stress disorder
E. The anxiety, worry, or physical symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning
F. The disturbance is due to the direct physiological effects of a substance or a general medical condition and does not occur exclusively during a mood disorder, psychotic disorder, or pervasive developmental disorder

GAD and chronic primary insomnia is that the former is associated with worries and pre-occupations on a wide variety of matters (including sleep), whereas worries in the latter condition are restricted to sleep itself.

Objective findings of sleep in GAD patients have been studied by means of polysomnography (PSG), actigraphy, and sleep logs. However, few studies have specifically focused on sleep in the elderly patient with GAD. Polysomnographic findings in GAD patients of different ages include: increased sleep latency, decreased total sleep time, decreased sleep efficiency, decreased amount of slow wave sleep, and increased arousal index [9, 10, 11, 12, 13]. These sleep findings, however, are neither sensitive nor specific for GAD. One study of older adults found that even in patients with subclinical levels of anxiety, increased wakefulness after sleep onset was still evident as measured by actigraphy and sleep log [14].

When comparing patients with GAD alone to patients with co-morbid GAD and depression, REM latency was shortened in the GAD/depressive group [15]. A comparison of patients with GAD alone versus primary depression alone found that the depressive group retained characteristics of decreased REM latency and increased percent of REM sleep [16]. Both GAD and primary dysthymia groups show a similar reduction in slow wave sleep [17].

Panic disorder

Definition and epidemiology

Patients with panic attacks complain of a range of physical and psychological symptoms. Chest pain, shortness of breath, tremors, nausea, and dizziness may occur, as well as fear of dying or depersonalization (the feeling of being detached from oneself). These symptoms have an abrupt onset and reach maximal intensity within 10 minutes. Panic attacks can occur both during the day and at night, with some studies suggesting that at least 30% of patients experience sleep-related attacks. When a patient fears recurrence of panic attacks or is afraid of potential consequences of the attacks, panic disorder is diagnosed (see Table 17.2).

Panic disorder has a lifetime prevalence of 4.7% and a prevalence in the elderly of 1% [2, 3, 18]. Panic disorder only rarely starts in later life; the presence of new panic symptoms in an elderly patient may suggest a depressive disorder, medical illness, or medication that could be a contributing factor [19].

Co-morbid depression and social phobia has been found in elderly patients with panic disorder, particularly with an age of onset earlier than 59 years; later onset of the disorder is associated with medical co-morbidities, such as chronic obstructive pulmonary

Table 17.2. DSM-IV-TR criteria for a panic attack

A discrete period of intense fear or discomfort, in which four (or more) of the following symptoms develop abruptly and reach a peak within 10 minutes:
(1) Palpitations, pounding heart, or accelerated heart rate
(2) Sweating
(3) Trembling or shaking
(4) Sensations of shortness of breath or smothering
(5) Feeling of choking
(6) Chest pain or discomfort
(7) Nausea or abdominal distress
(8) Feeling dizzy, unsteady, lightheaded, or faint
(9) Derealization (feelings of unreality) or depersonalization (being detached from oneself)
(10) Fear of losing control or going crazy
(11) Fear of dying
(12) Parasethesias (numbness or tingling sensations)
(13) Chills or hot flushes
N.B. A panic attack is not a codable disorder; a diagnosis is made as panic disorder with or without agoraphobia
Agoraphobia is defined as:
A. Anxiety about being in places or situations from which escape might be difficult (or embarrassing) or in which help may not be available in the event of having an unexpected or situationally predisposed panic attack or panic-like symptoms
B. The situations are avoided (e.g. travel is restricted) or else are endured with marked distress or with anxiety about having a panic attack or panic-like symptoms, or require the presence of a companion
C. The anxiety or phobic avoidance if not better accounted for by another mental disorder
DSM-IV-TR criteria for panic disorder without agoraphobia
A. Both (1) and (2):
(1) Recurrent unexpected panic attacks
(2) At least one of the attacks has been followed by 1 month (or more) of one (or more) of the following:
(a) Persistent concern about having additional attacks
(b) Worry about the implications of the attack or its consequences (e.g. losing control, having a heart attack, "going crazy")
(c) A significant change in the behavior related to the attacks
B. Absence of agoraphobia
C. The panic attacks are not due to the direct physiological effects of a substance (e.g. a drug of abuse, a medication) or a general medical condition (e.g. hyperthyroidism)
D. The panic attacks are not better accounted for by another mental disorder, such as social phobia, specific phobia, obsessive-compulsive disorder, post-traumatic stress disorder, or separation anxiety disorder

disease and Parkinson's disease [20]. One study of elderly patients found that 29% had co-morbid major depressive disorder and 17% had co-morbid social phobia [21].

Some studies have focused on establishing differences between nocturnal and daytime panic sufferers. Patients with nocturnal panic attacks have been found to have increased sensitivity to anxiety, experience attacks of longer duration, and report increased frequency of somatic symptoms [22, 23]. Although panic attacks during sleep occur less frequently than do panic attacks during wakefulness [24], some patients experience recurrent sleep-related episodes.

Effects on sleep

Subjectively patients with panic disorder may complain of insomnia, with sleep initiation and maintenance

difficulties [25]. In one study of panic disorder patients, 26% complained of multiple awakenings in the preceding month due to breathing difficulty as opposed to no such complaints in healthy controls. These patients also demonstrated greater overall sleep disturbance, as measured by higher scores on the Pittsburgh Sleep Quality Index [26].

On polysomnography decreased sleep continuity, decreased sleep efficiency, and increased sleep latency have been noted [27, 28, 29]. Changes in REM sleep among panic disorder patients remain controversial. While some studies maintain that no REM changes exist, another study found increased REM latency on the night of the sleep panic attacks [27, 28, 30]. Decreased REM latency typically found in major depression was not seen in a study of patients with co-morbid panic disorder and depression [31].

Panic attacks during sleep have been found to arise from NREM sleep, specifically during the transition from stage 2 to slow wave sleep [28, 29]. A movement analysis of patients with nocturnal panic found that these individuals moved less on the night of attacks as opposed to healthy controls; this finding held true as well in comparison to daytime panic and social phobic patients, although not to a statistically significant degree [32].

Obsessive-compulsive disorder

Definition and epidemiology

The defining characteristic of obsessive-compulsive disorder (OCD) is the presence of distressing obsessions or compulsions that an individual recognizes as excessive. The obsession or compulsion may be time consuming, lasting more than an hour a day, and impairment in social or occupational functioning is not uncommon. An obsession is characterized by a recurrent, intrusive thought, impulse, or image that can not be suppressed despite the individual's best efforts (e.g. thoughts or images of harming another). A compulsion is a repetitive behavior that occurs in response to an obsession or which has rigidly applied rules (e.g. checking or cleaning). The performance of a compulsion is directed at decreasing distress or preventing an unwanted outcome (Table 17.3). For instance, a recurrent fear of germ contamination (an obsession) may prompt an individual to scrub his or her hands methodically several times an hour (a compulsion), and thus prevent that person from being able to fully interact in a social context. In this situation impaired work functioning would also probably result due to the mental and physical strain of OCD. Despite

Table 17.3. DSM-IV-TR criteria for obsessive-compulsive disorder

A. Either obsessions or compulsions
Obsessions as defined by (1), (2), (3), and (4):
(1) Recurrent or persistent thoughts, impulses, or images that are experienced, at some time during the disturbance, as intrusive and inappropriate and that cause marked anxiety or distress
(2) The thoughts, impulses, or images are not simply excessive worries about real-life problems
(3) The person attempts to ignore or suppress such thoughts, impulses, or images, or to neutralize them with some other thought or action
(4) The person recognizes that the obsessional thoughts, impulses, or images are a product of his or her own mind (not imposed from without as in thought insertion)
Compulsions as defined by (1) and (2):
(1) Repetitive behaviors (e.g. hand washing, ordering, checking) or mental acts (e.g. praying, counting, repeating words silently) that the person feels driven to perform in response to an obsession, or according to rules that must be applied rigidly
(2) The behaviors or mental acts are aimed at preventing or reducing distress or preventing some dreaded event or situation; however, these behaviors or mental acts either are not connected in a realistic way with what they are designed to neutralize or prevent or are clearly excessive
B. At some point during the course of the disorder, the person has recognized that the obsessions or compulsions are excessive or unreasonable
C. The obsessions or compulsions cause marked distress, are time consuming (take more than 1 hour a day), or significantly interfere with a person's normal routine, occupational (or academic) functioning, or usual social activities or relationships
D. If another axis I disorder is present, the content of the obsessions or compulsions is not restricted to it
E. The disturbance is not due to the direct physiological effects of a substance or a general medical condition

the individual's best efforts to rid the mind of contamination fears or to stop washing their hands, he or she finds it difficult, even though he/she realizes the unreasonableness of the situation.

The lifetime prevalence of OCD is 1.6% [2]. Prevalence of OCD in the elderly is much less common than GAD, at only 0.6% [3]. The course of untreated OCD is usually chronic with rare remissions [33]. One study found that elderly OCD patients had a later age of onset than their younger counterparts. In addition, the most common presentations for the elderly centered around hand washing and fear of having sinned, as opposed to counting rituals [34].

Effects on sleep

Few studies have examined the effects of OCD on sleep, with even more limited data about sleep in the elderly. While some studies have shown decreased REM latency and decreased slow wave sleep, other studies contend that OCD patients do not differ from normal controls with respect to polysomnography [35, 36, 37, 38, 39].

One possible explanation for the difference in results could be the presence of co-morbid depression and OCD in some of the patient populations, as seen in the Insel and Hohagen studies [40]. Depression is found as a co-morbid condition in 33–39% of patients with OCD; these patients may also exhibit more severe mood or anxiety disorder psychopathology [41, 42]. Thus, it has not been clearly demonstrated that isolated OCD leads to distinct sleep changes. Furthermore, conclusions about sleep changes in elderly patients with OCD can not be drawn given the limited evidence available.

Treatment of anxiety and sleep disorders

Treatment of patients with anxiety and sleep disorders should be tailored to the individual. Medications such as selective serotonin reuptake inhibitors (SSRIs) or selective serotonin/norepinephrine reuptake inhibitors (SNRIs) can be employed as first line treatments for many anxiety disorders, including GAD, panic disorder, OCD, and PTSD. In contrast, the use of benzodiazepines in elderly patients is less clear, as this medication class has been associated with an increased risk of falls and fractures [43]. The possibility of substance abuse or dependence with benzodiazepine must also be taken into consideration. One study that examined the usage pattern of SSRIs/SNRIs versus benzodiazepines in patients with panic disorder, social phobia, and GAD found that after 9 years more than 50% of the patients continued on benzodiazepines compared to 35% who used SSRIs/SNRIs [44]. The risk/benefit profile of these medications must therefore be carefully weighed prior to implementation.

Adequate control of the underlying anxiety disorder is also an important component of patient therapy. The individual with persistent GAD may predictably complain of insomnia; treatment that focuses on improving symptoms of GAD may therefore have a positive effect on insomnia as well. One study that examined the effects of eszopiclone co-adminstered with escitalopram in patients with co-morbid GAD and insomnia found that the combination of medications led to greater improvements in anxiety, mood, and sleep quality when compared to patients who took escitalopram alone [45].

Patients who are taught the principles of cognitive behavioral therapy (CBT) may learn to apply them in the treatment of both anxiety disorders and insomnia. Insomnia can also be specifically targeted through education about sleep hygiene, sleep restriction, and the effects of substance use on sleep. Thus, the ideal treatment plan might include an array of therapies deemed relevant for the individual: medication, CBT, and patient education.

Major depressive disorder

Definition and clinical presentation

Major depressive disorder (MDD), is defined as a 2-week period during which depressed mood or lack of pleasure in activities (anhedonia) is accompanied by the following symptoms: feelings of guilt, fatigue, decreased concentration, changes in appetite, insomnia or hypersomnia, psychomotor agitation or retardation, and/or suicidal ideation (Table 17.4). A study of elderly medical inpatients found that a review of depressed mood, anhedonia, and persistence of depressive symptoms for at least 6 months aided in the diagnosis, as opposed to somatic symptoms, which are common to many medical and psychiatric disorders [46].

Elderly individuals may not volunteer information about depression or insomnia and may consequently go undiagnosed and untreated. A study of elderly assisted-living facility residents found that a majority of patients never reported depression to medical staff; however, if adequate communication between patient and staff took place, pharmacotherapy was initiated [47]. This

Table 17.4. DSM-IV-TR criteria for major-depressive disorder

A. Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure
(1) Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g. feels sad or empty) or observation made by others (e.g. appears tearful)
(2) Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation made by others)
(3) Significant weight loss when not dieting or weight gain (e.g. a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day
(4) Insomnia or hypersomnia nearly every day
(5) Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down)
(6) Fatigue or loss of energy nearly every day
(7) Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick)
(8) Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others)
(9) Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide
B. The symptoms do not meet criteria for a mixed episode
C. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning
D. The symptoms are not due to the direct physiological effects of a substance or a general medical condition
E. The symptoms are not better accounted for by bereavement, i.e. after the loss of a loved one, the symptoms persist for longer than 2 months or are characterized by marked functional impairment, morbid preoccupation with worthlessness, suicidal ideation, psychotic symptoms, or psychomotor retardation

finding highlights the need to proactively screen patients for depression.

Epidemiology, risk factors, and clinical significance

The lifetime prevalence of MDD is 16.6% [2]. The prevalence of MDD in the elderly is between 1% and 3% [48, 49]. A meta-analytical study of depression in the elderly identified the following risk factors: disability, new medical illness, prior history of depression, poor health status, poor self-perceived health, bereavement, female sex, disability, and sleep disturbance [50]. In particular, greater medical burden has been found to be independently associated with depression in the elderly [51].

A bidirectional connection between depression and sleep disturbance may exist: not only does depression increase the risk of insomnia but insomnia also may increase the risk of future depression [52]. In non-depressed elderly individuals, the best predictor of future depression was a current sleep disturbance such as insomnia [53]. Insomnia in the elderly has also been associated with an increased self-report of current depression and anxiety [54].

Depression comes at a significant cost to the individual and to society. The presence of untreated depression has been linked to increased morbidity and mortality, with a concomitant increase in medical costs from chronic disease [55]. Increased risk of death by cardiovascular disease has been found in depressed males [56].

The presence of depression and sleep disturbances has also been linked to increased benzodiazepine use in nursing home residents [57]. In addition, elderly individuals that require medication for depression or insomnia report a lower quality of life [58]. Suicide in the elderly is also a serious concern. Elderly individuals have been shown to use more violent methods when attempting suicide than their younger counterparts [59].

Subjective sleep symptoms

Patients with depression commonly complain of insomnia, which can include difficulty with sleep initiation, sleep maintenance, early morning awakening,

and non-refreshing sleep. Early morning awakening is particularly common in depression among the elderly [60], underscoring the potential yield in using sleep disturbance as one of the screening questions for depression. A study of African-American elderly individuals found that 45% of subjects reported sleep reinitiating times of greater than 30 minutes, while 14% of the men and 23% of the women had initial sleep latencies exceeding this time frame [61]. Even with treatment, insomnia may not easily remit in depressed individuals [62].

Daytime sleepiness has also been associated with depression in the elderly [63, 64]. In particular, men with more severe depression were more likely to complain of daytime sleepiness [65]. Excessive napping has also been linked to greater risk of mortality in older individuals with pre-existing cognitive impairment [66].

Objective sleep findings

Major depressive disorder has been associated with three major types of PSG effects: sleep continuity disturbances, slow wave sleep reduction, and REM sleep changes [67]. Sleep continuity changes in depression are characterized by increased wakefulness, sleep fragmentation, and decreased sleep efficiency [68]. Increased sleep onset latency and decreased total sleep time may also be seen [69].

Second, depressed patients may show a reduction in stages 3 and 4 of sleep, or slow wave sleep. Studies that have compared depressed patients to healthy controls have found decreased slow wave activity amplitude in the depressed group, a finding that is particularly striking in depressed men. In addition, the distribution of slow wave sleep may be abnormal in male patients with MDD: decreased slow wave activity occurred primarily during the first NREM period. Delta power and amplitude in this group demonstrated decreased accumulation and more gradual dissipation across NREM sleep when compared to both controls and depressed women [70, 71, 72, 73]. These findings suggest impairment in slow wave sleep regulation, particularly among depressed men.

Third, depressed patients may demonstrate REM sleep changes [68, 74]. Decreased REM sleep latency, prolonged first REM sleep period, increased REM density, and increased REM sleep percentage can be seen in this patient population [75]. Decreased REM latency is particularly prominent in depressed men [76]. Studies of patients with MDD found that a sleep profile of decreased REM latency, increased REM density, and decreased sleep efficiency effectively discriminated depressed individuals from healthy controls [77]. Although depressed patients have PSG sleep changes relative to age-matched controls across the adult lifespan, these depressed-control differences are more prominent among older adults.

Treatment of depression and sleep disorders

Both psychotherapy and pharmacotherapy continue to be viable treatment options for elderly patients suffering from depression. Cognitive behavioral therapy (CBT) for insomnia can have a positive effect on insomnia in individuals with mood disorders [78, 79]. Interpersonal therapy (IPT) can also effectively treat older patients with a major depressive disorder [80].

Practitioners and patients can jointly pick from a range of antidepressant medications, including SSRIs, SNRIs, tricyclics, and monoamine oxidase inhibitors. With elderly patients careful review of co-morbid medical conditions and possible side effects is necessary. A tricyclic medication, for instance, may be contraindicated in a patient with a recent history of myocardial infarction. Orthostatic hypotension with tricyclic antidepressants should also be considered.

Practitioners who treat elderly patients should be aware of the co-morbid nature of insomnia and depression. The ideal practice model is therefore to treat both conditions [81]. One study that evaluated the effects of eszopiclone co-administered with fluoxetine in middle-aged patients with co-morbid insomnia and major depressive disorder found that co-therapy led to improvement in both mood and sleep quality parameters [82]. Discontinuation of eszopiclone in patients on either fluoxetine or placebo did not lead to withdrawal or rebound insomnia. Reductions in depressive systems were also maintained after eszopiclone discontinuation [83].

Conversely, depression that manifests with hypersomnia may also occur and should be addressed. Stimulants such as amphetamines and modafanil are not FDA-approved but have been investigated as adjunctive medications for treatment of depression [84]. One study that examined the effect of modafinil on hypersomnic, non-elderly patients with MDD who were partial responders to SSRI therapy found that those on modafinil may experience an improvement in both wakefulness and mood [85].

Table 17.5. Treatment options for sleep disturbances co-morbid with anxiety and depressive disorders

Treatment option	Target symptoms	Comments
1. SSRI, SNRI antidepressants (examples: fluoxetine, sertraline, paroxetine, fluvoxamine, citalopram, escitalopram, venlafaxine, desvenlafaxine, duloxetine)	Anxiety and/or depressive disorder	• Wide range of available drugs • Generally well-tolerated in the elderly • Unlikely to directly improve insomnia or excessive sleepiness • Side effects may include insomnia, dream disturbances, restless legs syndrome, REM sleep behavior disorder
2. Sedating tricyclic antidepressants (examples: doxepin, amitriptyline)	Insomnia (at low doses); anxiety and/or depressive disorder (at higher doses)	• Low doses may be useful to treat insomnia • Higher doses required to have significant effect on anxiety, depression • Side effects are dose related and may include significant sedation, anticholinergic effects, orthostatic hypotension, cardiac conduction effects (e.g. prolonged QT_c), lethal overdose, weight gain, cognitive impairment
3. Other antidepressants (examples: mirtazapine, trazodone)	Insomnia (at low doses); anxiety and/or depressive disorder (at higher doses)	• Low doses may be useful to treat insomnia • Higher doses required to have significant effect on anxiety, depression • Side effects are dose related and may include significant sedation, orthostatic hypotension, cardiac effects (e.g. ventricular ectopy), lethal overdose, priapism, weight gain, cognitive impairment
4. Benzodiazepines (examples: alprazolam, lorazepam, diazepam)	Anxiety symptoms; insomnia symptoms	• Have sedative-hypnotic, anxiolytic, and myorelaxant properties • Individual agents vary widely in half-life, duration of action • Potential for physiological dependence and abuse • Side effects dose related and may include sedation, balance problems and falls, cognitive impairment
5. Benzodiazepine receptor agonist hypnotics (examples: zolpidem, zaleplon, eszopiclone)	Insomnia	• Less anxiolytic activity than benzodiazepines, especially drugs with selectivity for α_1-containing GABA receptors • Shorter half-lives than many benzodiazepines • Potential for physiological dependence and abuse • Side effects are dose related and may include sedation, balance problems
6. Medication combinations (examples: SSRI/SNRI + low-dose trazodone; SSRI/SNRI + benzodiazepine or BZRA)	Anxiety and/or depressive disorder, insomnia	• Medication combination may provide effective management of both psychiatric and sleep disorders • May permit lower doses of sedating antidepressant (e.g. trazodone, tricyclic) • Permits separate titration of anxiolytic/antidepressant and insomnia medications • Potential for side effects from both medication classes
7. Stimulant medications (examples: methylphenidate, modafinil)	Daytime sleepiness; adjunct to antidepressant	• May improve alertness in patients with anergic depression • Should rule-out sleep apnea prior to treatment for patients with significant daytime sleepiness • Side effects dose dependent and may include agitation, insomnia, psychosis, hypertension, cardiac conduction problems

Table 17.5. (*cont.*)

Treatment option	Target symptoms	Comments
8. Psychotherapy (examples: cognitive behavioral therapy, interpersonal psychotherapy, problem-solving therapy)	Depression, anxiety	• Various specific psychotherapies have demonstrated efficacy for depression and anxiety disorders • Little specific focus on sleep problems in most traditional psychotherapies
9. Cognitive behavioral therapy for insomnia	Insomnia	• Small studies suggest efficacy in patients with co-morbid depressive and anxiety disorders, but with smaller effect size than in primary insomnia • May be combined with pharmacotherapy or psychotherapy for depression, anxiety disorders

Conclusion

Both subjective sleep complaints and objective findings have been reported in elderly patients with anxiety and depressive disorders. A strong interplay exists between these underlying psychiatric disorders and sleep disturbances. Patients with depressive and anxiety disorders may complain of insomnia, while in turn insomnia may increase the risk of developing a psychiatric disorder. To address this interplay, treatment with either pharmacotherapy or psychotherapy may focus on both the sleep disturbances and mood or anxiety disorders to achieve optimal benefit (Table 17.5).

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Part 3
Chapter
18

Sleep disorders in the elderly

Sleep in Parkinson's disease

Aleksandar Videnovic and Cynthia L. Comella

Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disorder affecting about 300 per 100 000 people. Motor hallmarks of the disease are tremor, rigidity, bradykinesia, and impaired balance. Non-motor symptoms of PD are a prominent cause of disability in the PD population, and may even have a greater impact on the quality of life than the motor symptoms themselves. Sleep dysfunction, initially recognized by James Parkinson in his famous monograph "An essay on the shaking palsy," is one of the most striking non-motor symptoms of PD. It is only recently that sleep disturbances in PD have received the attention of the medical and research community. This was steered by several important observations. Frucht and colleagues reported *sleep attacks* in PD patients treated with dopamine agonists, drawing attention to daytime sleepiness in PD [1]. Observations that REM behavior disorder (RBD) may be an indicator of pre-symptomatic PD opened a window of opportunity to explore early markers of the disease, which are so vital to the development of neuroprotective therapies [2]. Recent studies of the hypothalamic hypocretin system dysfunction in PD proposed a novel and exciting hypothesis of the pathophysiology of sleep dysfunction in PD that may further translate into a better understanding of the neurodegenerative process of PD [3]. In this chapter we review sleep disorders associated with PD.

Disorders of nocturnal sleep in PD

Disturbed nocturnal sleep is frequently reported by PD patients and/or their relatives/care-givers. In a study of 239 patients with PD, 60% of patients reported sleep problems compared with 45% of patients with diabetes and 33% of healthy controls [4]. It is estimated that during the course of disease up to 90% of PD patients will experience problems with overnight sleep [4, 5, 6]. Sleep disruption occurs from the onset of PD, but disease progression remains a key factor in the worsening of sleep disabilities in PD [7]. This supports the concept that the underlying dopaminergic deficit plays a crucial role in sleep dysfunction linked to PD. The most common sleep disorders in PD include insomnia, REM sleep behavior disorder (RBD), sleep apnea, restless legs syndrome (RLS), and periodic limb movement disorder (PLMD) [8].

Sleep fragmentation in PD

Insomnia is the most common sleep disturbance in the general population, and can be classified as sleep initiation insomnia, sleep fragmentation, and early awakening. Patients with PD suffer mainly from sleep fragmentation and early awakenings. These symptoms affect up to 60% of patients. Data on the development of insomnia in patients with PD are limited. In a longitudinal, cohort study of 213 PD patients that were followed over an 8-year period, the frequency of insomnia remained high, and varied considerably in individual patients over time [9]. This is in agreement with studies of insomnia in the elderly, where specific timely treatments result in individual fluctuations of insomnia over time. It is therefore important to recognize and address PD-specific causes of insomnia and sleep fragmentation early on.

The causes of sleep disruption in patients with PD are related to aging, the PD neurodegenerative process itself, medication regimens, motor dysfunction, neuropsychiatric symptoms, inadequate sleep hygiene, urinary difficulties, and co-existing sleep disorders.

The re-emergence of motor PD symptoms during the night is a common cause of sleep fragmentation. Although the motor symptoms of PD may diminish during sleep, electrophysiological studies have shown a recurrence of tremor in the later stages of sleep [10], increased muscle activity [11], akathisia [12], painful dystonia, and dyskinesias [13]. Difficulties with turning in bed overnight are commonly identified causes of sleep disruption in PD [14]. Treatment with levodopa may improve these night-time symptoms [15].

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Similar improvements have been observed with apomorphine and cabergoline [16, 17].

Although antiparkinson medications may improve nocturnal sleep due to PD symptoms, they may also cause sleep disruption and alter sleep architecture [18]. Levodopa has been shown, at least acutely, to alter REM sleep, and give rise to vivid dreams [19]. The direct dopamine agonists may increase nocturnal activity, as assessed using polysomnography or actigraphy [18]. Vivid dreaming, nightmares, and hallucinations are causes of frequent awakenings in a subset of PD patients [20].

Nocturia is one of the most common overnight symptoms that significantly contributes to sleep maintenance insomnia in patients with PD. Nocturia is less commonly reported in patients treated with dopamine agonists, suggesting possible benefits of D1/2 receptors activation on detrusor hyper-reflexia [21].

REM sleep behavior disorder (RBD) and REM sleep without atonia (RSWA) in PD

REM behavior disorder (RBD) is a parasomnia, first described by Schneck and colleagues in 1986 [22]. The salient features of RBD include excessive muscle tone and the occurrence of dream enactment behaviors during REM sleep [23]. REM sleep without atonia (RSWA) refers to the electrophysiological finding of loss of EMG atonia during REM sleep in the absence of dream enactment behavior. It is sometimes labeled as a *subclinical* or *pre-clinical* RBD [24]. REM behavior disorder can be idiopathic, or co-exist with other neurological, mainly neurodegenerative disorders [25].

Epidemiology

The estimated prevalence of RBD in the elderly is about 0.5%, with men representing more than 90% of all cases. RBD and RSWA are more frequent in patients with parkinsonian disorders, including multiple systems atrophy and dementia with Lewy bodies [24, 25, 26, 27, 28], than in idiopathic PD. The reported prevalence of RBD in the PD population is 15–50% [29, 30, 31] (Table 18.1). This variability is the result of selection and referral patterns, as well as different methods of RBD ascertainment. In the absence of polysomnography, clinically insignificant RBD and RSWA associated with PD are not captured, leading to underestimation of actual prevalence of RBD among the PD population. Similar to the idiopathic form, RBD in PD is more common in men than women [31]. It has been suggested that RBD may be associated with longer disease duration and higher daily doses of dopaminergic medications [32].

A parkinsonian syndrome may develop in about 40% of patients diagnosed with RBD [33], and about 50% of patients with co-existent RBD and a neurodegenerative disorder report the onset of RBD prior to the clinical onset of their neurodegenerative disorder [34]. The most comprehensive assessment of the natural progression of RBD reveals that 12 years after the RBD onset, 45% of patients with idiopathic RBD developed a neurodegenerative disorder, most commonly PD, followed by Lewy body disease and multiple system atrophy (MSA) [35].

Pathophysiology

Several neurological abnormalities, such as cortical EEG slowing, subtle neuropsychological deficits, autonomic dysfunction, and decreased striatal dopaminergic innervation have been reported in patients with idiopathic RBD, suggesting that RBD may be a pre-clinical stage of a developing synucleinopathy [36]. Patients with idiopathic RBD have similar olfactory deficits and visual impairments to patients with idiopathic PD, suggesting that in some patients RBD may be a harbinger of PD [2]. Several epidemiological studies demonstrated that RBD may precede motor and cognitive symptoms of synucleinopathies [34, 35]. In contrast, RBD usually evolves in concert with or after the onset of parkinsonism among non-synucleinopathy disorders. This differential expression of RBD supports the concept of selective vulnerability occurring in key brainstem neuronal networks in the synucleinopathies [37].

The anatomical areas involved in RBD include the pedunculopontine nucleus (PPN), locus coeruleus and sub-coeruleus complex, gigantocellular reticular nucleus, and dorsal raphe [25]. It has recently been proposed that neurodegeneration in PD initially occurs in the olfactory and lower brainstem areas, with subsequent spread to the substantia nigra and neocortex [38]. These pathological findings provide a rationale for the emergence of RBD prior to the onset of motor symptoms of PD. Imaging studies further support the link between RBD and PD. ^{123}*N*-(3-iodopropen-2-yl)-2β-carbo-methoxy-3β-(4-chlorophenyl) tropane single photon emission computed tomography (^{123}IPT-SPECT) imaging reveals a progressive reduction of striatal dopamine transporters along the continuum of normal controls, subclinical RBD, clinically manifest RBD, and PD

Table 18.1. Prevalence of the REM sleep behavior disorder (RBD) in Parkinson's disease (PD)

			Subjects (N)		Prevalence (%)		
Study	**Design**	**Methods**	**PD**	**Controls**	**PD**	**Controls**	**Comments**
[9]	Prospective longitudinal cohort (8 years)	Semi-structured interview Sleep questionnaire	231	NA	15–27 in 8 years	NA	– RBD varied over time – RBD was associated with male gender, less parkinsonism, and higher levodopa dose
[109]	Cohort	Questionnaire Structured interview	289	NA	27	NA	– Presence of RBD was associated with an increased risk of hallucinations and delusions – RBD preceded PD in 37% of subjects
[110]	Cohort (PD patients with Park2 mutation)	PSG	10	NA	60	NA	– RBD followed the onset of PD in all subjects
[31]	Cohort	Questionnaire	195	NA	33	NA	– RBD onset was before PD in 25% of subjects – RBD was associated with male gender, age, and PD duration
[30]	Case/ control	PSG Structured interview	33	16	33	0	– Sensitivity of clinical diagnostic criteria for RBD in PD was 59% – REM sleep without atonia was present in 58% of PD subjects, and in 6% of controls
[29ref 29]	Cohort	Questionnaire	61	NA	15	NA	– 33% of subjects with RBD reported injuring themselves or their care-giver during sleep

NA, not applicable; PSG, polysomnography; RBD, REM sleep behavior disorder.

[39, 40], suggesting that reduced striatal dopamine transporters may be a pathophysiological mechanism of RBD. Recent observations of the restoration of motor control in PD during REM suggest that abnormal behavioral manifestations during the RBD may be generated by the motor cortex, and follow the pyramidal tract bypassing the extrapyramidal system. [41].

RBD is not specific for PD, and occurs more frequently in other parkinsonian disorders, including multiple system atrophy and dementia with Lewy bodies [42]. Although there is a strong association between RBD and synuclein diseases, RBD has been documented in patients with tauopathies, such as progressive supranuclear palsy, Alzheimer's disease, and corticobasal degeneration [25].

A strong association of RBD and neurodegenerative disorders, in particular PD, provides a rationale for a longitudinal study of RBD patients, with the aim to identify markers that will predict the progression of RBD towards PD. This can be fundamentally important for the development of neuroprotective treatment strategies.

Clinical features

The clinical features of RBD in PD range from nocturnal vocalizations to complex, vigorous behaviors [29]. These behavioral manifestations may be sufficiently violent to cause injuries to patients and/or bed partners, including ecchymosis, lacerations, fractures, and dislocations [29]. RBD may also occur during naps [41],

and fluctuate in frequency and severity, often occurring sporadically [43]. Episodes of RBD happen after the first hours of sleep, when REM periods begin, and become more frequent in the early hours of the morning coinciding with more prolonged REM periods. Normalization of a movement strength, speed, and smoothness, as well as normalization of speech and facial expression during RBD in patients with PD has been recently reported [41]. This is suggestive of a transient restoration of motor control during RBD.

The co-existence of RBD and PD is associated with a three-fold increased risk of hallucinations or delusions. Up to 50% of PD patients with RBD have hallucinations [43]. The pathophysiological substrate for hallucinations in PD is poorly understood. It has been proposed that degeneration of brainstem areas involved in the regulation of REM sleep may be the main cause of hallucination in PD [44]. The presence of co-existent hallucinations and RBD is associated with a more pronounced cognitive impairment affecting short- and long-term memory, logical abilities, and frontal function in PD patients [45]. This is suggestive of a common neurobiological substrate for RBD, hallucinations, and cognitive dysfunction.

Diagnosis

Based on the most recent International Classification of Sleep Disorders, polysomnography is mandatory for the diagnosis of RBD. Sleep disorders such as sleepwalking, night terrors, obstructive sleep apnea, and sleep-related seizures may have manifestations similar to RBD, and polysomnography plays a critical role in separating these disorders from RBD. Furthermore, polysomnography is the only method to detect RSWA. Polysomnographic findings of RBD in PD include excessive submental or limb EMG activity, limb jerking, and dream enactment during REM sleep.

Treatment

Controlled, randomized, double-blind trials for the treatment of RBD in the PD population are lacking. Clonazepam in small doses (0.25–1 mg) is the most common treatment [46]. The use of clonazepam may be limited due to the development of daytime somnolence. Clonazepam may further aggravate apneas in patients with co-existent sleep apnea/hypopnea syndrome. Donepezil, pramipexole, and levodopa have also been shown to be effective, although the experience is limited to case reports [47, 48]. Melatonin has been reported to be effective at a dose range of 3–12 mg [49]. Tricyclic antidepressants, serotonin, and norepinephrine re-uptake inhibitors may induce RBD symptoms [20]. Patients' bed partners should be counseled on the nature of RBD and self-protective measures in medically refractory cases.

Sleep disordered breathing in PD

Sleep disordered breathing has not been extensively studied in the PD population (Table 18.2). Initial reports of irregular respiratory patterns with nocturnal worsening and central hypoventilation come from patients with post-encephalitic parkinsonism [50]. Sleep disordered breathing is less prevalent in idiopathic PD than in other parkinsonian disorders such as multiple system atrophy [51].

Obstructive sleep apnea/hypopnea syndrome (OSAHS) is the most common type of sleep disordered breathing. The reported prevalence of OSAHS in PD is higher than in the general population but the epidemiological data is limited. In a study of 54 PD patients, 25% had significant sleep apnea with an apnea/hypopnea index (AHI) >20, compared with 2.5–4.4% of the non-parkinsonian elderly population [52]. Other studies, however, did not find a higher prevalence of sleep apnea in PD patients [53, 54]. These differences in the prevalence of OSAHS in the PD population can be a result of referral biases and methodologies used to ascertain the disorder.

While obstructive sleep apnea represents the most common form of sleep apnea syndrome in the general population, obstructive, central, and mixed apneas may be equally represented in PD patients [53]. In most PD series, the apnea index is mild to moderate. Obesity, a strong predictor of OSAHS in the general population, is not predictive of this disorder in the PD population since most PD patients with OSAHS have normal body mass indices [52]. There is no clear relationship between the prevalence of sleep disordered breathing in PD and disease duration, severity, or PD medication regimen [55]. Sleep apnea may co-exist with RLS/PLMD or RBD [56].

Polysomnography is required to evaluate the presence and severity of sleep apnea and should be obtained in PD patients with excessive daytime somnolence (EDS) or a history suggestive of sleep apnea [57]. Continuous positive airway pressure (CPAP) is the treatment of choice for obstructive sleep apnea (OSA). This treatment has not been systematically studied

in the PD population. Several surgical approaches (uvulopalatopharyngoplasty, removal of enlarged tonsils and adenoids) and orthodontic appliances may be considered for patients who can not tolerate CPAP.

Restless legs syndrome and periodic limb movement disorder in PD

Restless legs syndrome (RLS), initially described by Ekbom in 1945, is a common disorder affecting 0.1–15% of the general population. Several studies that addressed RLS in PD documented prevalence rates between 8% and 20% [58]. Although most studies report an association between RLS and PD, small cohorts and various ascertainment methodologies do not allow definitive conclusions (Table 18.3). Furthermore, associated iron deficiency confounds the data supporting increased prevalence of RLS among the PD population. Periodic limb movement disorder, initially described by Lugaresi in 1967 as nocturnal myoclonus, may co-exist with RLS or occur independently. This disorder affects 30–80% of PD patients [59], and may be more common in advanced PD. An increased PLMD index has been recently reported in de novo, untreated PD patients, supporting the relationship between RLS and PD [7].

Dysfunction of dopaminergic systems, in particular the diencephalospinal pathway, has been implicated in the pathophysiology of RLS [60]. There is however no imaging or pathological evidence of dopaminergic cell loss in RLS [61, 62]. Clinical and neuroimaging studies have failed to demonstrate that RLS precedes the diagnosis of PD [63].

PD patients with RLS have more pronounced nocturnal sleep disturbances than PD patients without RLS [64]. The relationship between RLS/PLMD and EDS in PD has not been extensively studied. Available data show that somnolent PD patients do not have more frequent RLS or PLMD [65].

The diagnosis of RLS in PD patients may be confounded by akathisia and nocturnal motor symptoms. The presence of diurnal variations of symptoms in RLS, and the feeling of inner restlessness without a sensory component in akathisia, may help to differentiate akathisia from RLS.

Treatment of RLS in PD has not been evaluated in controlled studies. When these two conditions co-exist, the pharmacological approaches include dopamine agonists, anticonvulsant medications, opioids, and clonazepam. Dopamine agonists (ropinirole, pramipexole, cabergoline) remain the first-line therapy. Levodopa use for RLS should be avoided due to risks of rebound and augmentation. Tricyclic and selective serotonin re-uptake inhibitor antidepressants can worsen RLS and PLMD. While some reports on the impact of functional neurosurgery on RLS in PD document improvement in RLS, others found emergence of RLS after the surgery [66, 67].

Circadian rhythm dysfunction in PD

Disruption of circadian rhythms is a well-recognized cause of sleep fragmentation and daytime somnolence. Circadian rhythms have not been extensively studied in PD. Alterations in body temperature and cortisol synthesis in PD patients illustrate the circadian rhythmicity perturbations in PD. Only a few studies explored melatonin secretion patterns in PD patients, and found a slight phase advance and amplitude decrease of circadian melatonin secretion related to the evolution and treatment of PD [68, 69, 70]. Circadian rhythms have not been studied in PD patients in respect to co-existent sleep dysfunction. Characterizing circadian rhythms in this subgroup of patients could provide additional insight into the pathogenesis of daytime sleepiness and sleep dysfunction in PD. If there is a disturbance of circadian time keeping in PD, chronobiological therapeutic approaches, such as bright light therapy, may be a novel treatment choice for sleep–wake dysfunction in PD. Such behavioral strategies would be highly advantageous since pharmacological interventions for sleep disturbances in PD have been of modest benefit, and may cause unacceptable side effects. Preliminary studies of bright light treatment in the PD population documented improvements in motor symptoms, sleep, and mood [71, 72]. Further validation studies including larger cohorts and employing objective outcome measures are needed.

Disorders of daytime alertness in PD

Epidemiology

Excessive daytime somnolence (EDS) is common in the PD population (Table 18.4), affecting up to 50% of patients, compared to 1% of healthy elderly patients and 4% of patients with chronic medical conditions such as diabetes mellitus [73, 74]. The incidence of EDS increases with the progression of the disease. A longitudinal study of 142 PD patients demonstrated a 6% annual increase in EDS [9]. Duration and severity

Table 18.2. Prevalence of sleep disordered breathing (SDB) in Parkinson's disease (PD)

			Subjects (N)		SDB prevalence (%)		
Study	**Design**	**Methods**	**PD**	**Controls**	**PD**	**Controls**	**Comments**
[111]	Case/control	PSG	49	49	43	NA	– Retrospective analysis of PSG data – Controls were matched in terms of age, gender, and apnea/hypopnea index – PD subjects had less decline in oxygen saturation levels than controls – Obstructive, central and mixed apneas were equally present in PD subjects versus controls, who had mainly obstructive apneas
[55]	Case/control	PSG	15	15	73	33	– SDB is common in PD – SDB correlates with the severity of PD
[52]	Cohort	PSG MSLT	54	NA	20	NA	– Severity of sleepiness was not dependent on nocturnal sleep abnormalities, motor and cognitive impairment, or antiparkinsonian treatment – Obstructive apneas were the most common form of SDB
[54]	Cohort	PSG	11 mild PD/7 severe PD	NA	0	NA	– Apnea/hypopnea index was within normal limits in both groups – Oxygen saturation levels were not reported
[112]	Case/control	PSG Autonomic testing	26	15	31	27	– Prevalence of SDB in untreated PD subjects was similar to controls
[113]	Case/control	PSG	4 untreated PD/6 severe PD	20	24/49	11	– PD subjects had more frequent episodes of obstructive and central apneas than controls
[114]	Case/control	PSG	12	12	0	8	– No increase in sleep apneas was found among PD subjects

MSLT, Multiple Sleep Latency Test; NA, not applicable; PSG, polysomnography; SDB, sleep disordered breathing.

of PD, as well as male gender, have been variably associated with EDS [75, 76]. Two studies that assessed ethnicity-related differences in EDS in PD documented lower prevalence of EDS among the Asian PD population [77, 78].

EDS has not received appropriate medical attention until the emergence of reports of unexpected, sudden onset of sleep or "sleep attacks" in PD patients associated with motor vehicle accidents [1]. "Sleep attacks" were defined in the first descriptive study as

Table 18.3. Prevalence of the restless legs syndrome (RLS) in PD

			Subjects (N)		Prevalence (%)		
Study	**Design**	**Methods**	**PD**	**Controls**	**PD**	**Controls**	**Comments**
[115]	Cohort	PDSS ESS IRLSSG criteria	114	NA	22	NA	– Moderate severity of RLS in PD – Worse PDSS scores in PD with RLS – Absence of increased hypersomnolence in PD with RLS
[64]	Case/control	PSQI IRLSSG criteria	165	131	12	2	– PSQI score was higher in PD/RLS patients, compared with PD patients without RLS and controls – Higher prevalence of RLS than in Caucasians
[65]	Cohort	Questionnaire ESS	86	NA	50	NA	– RLS was investigated with a single question
[116]	Case/control	IRLSSG criteria ESS	126	128	8	1	– Depression was more prevalent among PD/RLS patients – Lower ferritin levels in PD/RLS patients
[117]	Case/control	Sleep questionnaire	149	115	14	1	– RLS was investigated with a single question
[97]	Cohort	Survey Interview IRLSSG criteria ESS	303	NA	21	NA	– Lower ferritin levels in PD/RLS patients
[118]	Cohort	IRLSSG criteria	125	NA	0	NA	– RLS prevalence in PD was similar to general population
[119]	Cohort	Survey	100	NA	17	NA	– RLS prevalence in PD was similar to general population

ESS, Epworth Sleepiness Scale; IRLSSG, International Restless Legs Syndrome Study Group; NA, not applicable; PSQI, Pittsburg Sleep Quality Index; PDSS, Parkinson's Disease Sleep Scale.

"events of overwhelming sleepiness that occur without warning or with a prodrome that is sufficiently short or overpowering to prevent the patient from taking appropriate protective measures" [1]. Whether sleep attacks represent a new sleep disorder or a culmination of pre-existing somnolence is still a matter of debate.

In a survey of 2952 PD patients, 6% had sleep attacks [79]. Some studies report the prevalence of sleep attacks in PD as high as 43% [80]. Wide differences in reported prevalence rates of sleep attacks are the result of various methods of ascertainment and a lack of standardized definition of sleep attacks. In order better to characterize the sudden onset of sleep, several categories of sudden sleepiness in PD have been proposed [79]. While the term "sleep attack" should be linked to the sleep episode that occurs without prior sleepiness or other warning signs, the term "sudden onset of sleep" should be used when not differentiating if there were any prior sleepiness or warning signs.

Sleep attacks have important safety implications. Episodes of falling asleep at the wheel have been reported in up to 23% of PD patients [75]. Based on a survey of 638 highly functioning PD patients, 420 of whom were drivers, 3.8% had at least one episode of sudden onset sleep while driving, and 0.7% had no warning [81]. In a survey of 5210 PD patients with a driver's license, 390 (8%) experienced sudden onset sleep at the wheel [82]. Of these patients 57% reported warning signs of sleepiness, while 26% had sudden onset sleep completely unexpectedly.

Etiology and pathophysiology

The etiology of EDS in PD is multifactorial. The primary neurodegenerative process of PD, complex medication

Table 18.4. Prevalence of excessive daytime sleepiness (EDS) and sudden onset sleep (SOS)/sleep attacks (SA) in Parkinson's disease

		Subjects (N)			EDS – prevalence (%)		SOS/SA prevalence (%)		
Study	Design	PD	Controls	Methods	PD	Controls	PD	Controls	Comments
[96]	Cohort	1629	NA	Questionnaire ESS	29	NA	0.5	NA	– Risk factors for EDS were male gender, reduced daily activity level, and high levodopa equivalents – Risk factors for SOS were ESS score >10, male gender, and low Hoenh and Yahr stage
[120]	Cohort	222	NA	Questionnaire ESS PSG MSLT	43.2	NA	6.8	NA	– Impaired vigilance was associated with nocturnal sleep disorders, dopaminergic medications – SOS was associated with severe sleepiness on the MSLT
[121]	Prospective 8-years cohort	89	NA	Structured interviews ESS	54	NA	NR	NA	– EDS was associated with age, gender, and use of DA – Progression of EDS: 5.6% (baseline); 22.5% (4 years follow-up); 40.8% (8 years follow-up)
[73]	Case/control	46	3	PSG MSLT ESS	50	NS	NR	NR	– No correlation was found between ESS, MSLT and clinical features
[122]	Case/control	176	174	Questionnaire ESS PSQI	33	16	27 (SA)	32 (SA)	– Levodopa therapy was the most consistent factor associated with SA – ESS had poor predictive value for SA (40%)
[123]	Case/control	22	16	ESS	59	31	NR	NR	– EDS was strongly associated with anxiety
[82]	Cohort	5210	NA	Questionnaire Structured interviews	NS	NA	8 (SOS)	NA	– Within subjects with SOS: 47% had unintended sleep episode only; 26% had SOS completely unexpectedly (sleep attack); 17% reported SOS with and without prior sleepiness; 2% of subjects had an accident due to the SOS – Risk factors for driving accidents:- disability caused by PD; increased EDS (higher ESS scores); SOS while driving

[80]	Cohort	6620	NS	Questionnaire ESS	33	NA	43 (SOS)	NA	– SOS occurred at least twice per week in 51% of subjects who experienced SOS – SOS occurred earlier in patients on non-ergoline DA – Younger patients on non-ergoline DA had increased risk for developing SOS – Strong correlation was found between SOS and ESS scores – Authors proposed several categories of daytime sleepiness
[124]	Cohort	22	NA	Sleep interview ESS Ambulatory PSG	36	NA	32 (SA)	NA	– Total nocturnal sleep was longer in subjects with SA – Two subjects had SA documented by ambulatory PSG
[125]	Cohort	80	NA	PSG MSLT MWT ESS	19	NA	NR	NA	– Total dopaminergic medication dose was best predictor of EDS – ESS did not correlate with MSLT, MWT
[65]	Cohort	86	NA	ESS Sleep questionnaire	32	NA	NR	NA	– Snoring was the most important risk factor associated with EDS
[78]	Case/control	53	17	ESS	NS	NS	NS	NS	– ESS score was higher in subjects with advanced disease – EDS in PD is milder in Japan than in USA/Europe
[126]	Case/control	99	44	ESS Sleep questionnaire	33	11	NR	NR	– EDS was associated with heavy snoring
[127]	Prospective 1-year study	25	NA	ESS PSQI	12/48 (1 year)	NA	NR	NA	– ESS increased significantly after 1 year of follow-up
[99]	Cohort	101	100	ESS Questionnaire	76	47	21 (SOS while driving)	6	– ESS scores and levodopa dose equivalents were predictive of SOS while driving – 4% of PD subjects with ESS score >15 did not appreciate sleepiness

Table 18.4. (*cont.*)

Study	Design	Subjects (N)		Methods	EDS – prevalence (%)		SOS/SA prevalence (%)		Comments
		PD	Controls		PD	Controls	PD	Controls	
[79]	Cohort	2952	NA	Questionnaire ESS	NS	NA	6 (SA)	NA	– 21% of subjects had SA while driving – 86% of subjects had SA at least once per week – SA frequency was independent of warning signs or higher ESS score – levodopa therapy conferred the lowest risk for SA, followed by therapies with DA, and DA + levodopa – Main factors associated with SA: ESS score, DA therapy, PD duration
[128]	Case/control	47	51	ESS MSLT	NS	NS	NS	NS	– 18 PD subjects did not perceive at least one nap – 4 PD subjects had a driving accident; 3 of them had nap misperception
[95]	Cohort	70	NA	Questionnaire	NS	NA	34 (SA)	NA	– No sleep episodes occurred without warning signs – EDS and early arousals were risk factors for irresistible daytime sleepiness
[85]	Case/control	149	115	ESS	21	3	NR	NR	– Higher ESS scores correlated with higher H&Y stage and higher UPDRS scores
[52]	Cohort	54	NA	PSG MSLT ESS	50	NA	NR	NA	– Sleep onset REM (narcolepsy-like) present in 39% of subjects – EDS did not correlate with DA therapy, disease duration, motor disability, and total sleep time
[129]	Cohort	75: 25 (de novo) 50 (on treatment)	25	ESS PSQI	12/74	4	NR	NA	– ESS/PSQI: de novo PD vs. controls were not different – ESS/PSQI : higher scores in treated PD vs. de novo PD + controls – No correlation between ESS and PSQI
[130]	Case/control	368	243	ESS	NS	NS	NR	NR	– Higher ESS score was associated with combination therapy regimen and longer disease duration

[131]	Case/control	201	241	ESS Questionnaire	20	10	14 (SA)	2	– SA during driving in 13.9% of PD subjects and 1.9% controls – SA associated with longer disease duration and higher levodopa dose equivalents – ESS score >10 had high sensitivity (88%) and specificity (71%) for predicting SA
[81]	Cohort	638	NA	ESS Inappropriate Sleep Composite Score	51	NA	4 (SOS)	NA	– 0.7 % of subjects with SOS while driving did not have any warning signs – Inappropriate Sleep Composite Score increased the specificity of ESS in capturing SOS
[75]	Cohort	303	NA	ESS National Sleep Foundation Survey Questionnaire	50	NA	23	NA	– EDS was associated with disease duration, male gender, use of any class of dopaminergic medications – SOS was associated with higher ESS score
[132]	Cohort	236	NA	Questionnaire	NR	NA	31 (SA)	NA	– SA was associated with first autonomic failure followed by therapy with DA
[84]	Case/control	27	13	PSG MSLT	37	NS	NR	NR	– Poor nocturnal sleep was associated with greater daytime alertness – 6 subjects had sudden onset REM sleep; those subjects were sleepier than others – No association was found between levodopa/pergolide use and EDS – Selegiline may be contributing to EDS and sudden onset REM sleep
[74]	Cohort	245	NA	Questionnaire	16	1	NR	NA	– ESD was associated with advanced stage, longer levodopa use, hallucinations, and cognitive decline

DA, dopamine agonist; EDS, excessive daytime sleepiness; ESS, Epworth Sleepiness Scale; MSLT, Multiple Sleep Latency Test; MWT, Maintenance of Wakefulness Test; NA, not applicable; NR, not reported; NS, not specified; PSG, polysomnography; PSQI, Pittsburg Sleep Quality Index; SA, sleep attack; SOS, sudden onset sleep.

regimens, age-related changes in the sleep architecture, and co-existent sleep disturbances play an important role in the development of EDS. Pathological studies indicate that the neurodegenerative process in PD originates in brainstem areas outside of the substantia nigra [38]. It is therefore likely that subtle non-motor features of PD, such as EDS, may precede the onset of motor symptoms. In the Honolulu-Asia Aging Study, there was more than a three-fold increase in the risk of developing PD in elderly men with EDS that could not be accounted for by any other factor, suggesting that EDS may be an early manifestation of extra-nigral degeneration [83]. The intrinsic role of the neurodegenerative process in EDS is further supported by the lack of poor nocturnal sleep in patients with EDS [44, 84], and by observed associations between EDS and more advanced PD [74, 81, 85].

The loss of the hypothalamic wake-promoting substance, hypocretin (orexin), underlies the development of sleepiness in narcolepsy. Hypocretin may function as a regulator of the "flip-flop" switch that regulates the sleep–wake cycle, as proposed by Saper and colleagues [86]. Initial studies of the hypocretin system in PD revealed conflicting findings; while some reported decreased ventricular hypocretin levels in advanced PD [87], others found normal concentrations in spinal CSF [88]. The most complete pathological study of the hypocretin system in PD found a reduction of hypocretin neurons, hypocretin tissue concentrations, and ventricular CSF hypocretin levels in PD patients compared to controls [3]. Although not replicated, these results are suggestive of a pathophysiological link between daytime somnolence and the hypocretin system in PD. Genetic associations of sleepiness in PD with catechol-*O*-methyltransferase genotypes [89] and (-909T/C) preprohypocretin polymorphisms [90] further support this hypothesis.

The use and dose of dopaminergic agents are consistent factors associated with an increased frequency of EDS. A comparison of daytime sleepiness among 50 treated, 25 untreated PD patients, and age-matched healthy controls identified dopaminergic agents to be the principal factor associated with EDS [56]. Approximately half of the untreated patients who went on to receive dopaminergic medications developed EDS within 1 year [91]. In two major double-blind, placebo-controlled clinical trials somnolence was reported in 32.4% of patients treated with pramipexole versus 17.3% of levodopa-treated patients, and in 27.4% of patients treated with ropinirole versus 19.1% of levodopa-treated patients [92, 93]. In patients treated with levodopa monotherapy EDS was present in 13.7% of patients [94]. Although some have suggested that the direct dopamine agonists (DAs) cause sleepiness as a class effect [95], in most studies the major predictive factor for EDS was not the specific type of dopaminergic agent, but rather the total dose or burden of dopaminergic therapy, including both levodopa and direct DA [81, 96]. Young PD patients may have an increased risk of developing sudden onset sleep shortly after the initiation of nonergoline DA [79]. Since these patients represent a major driving force among the PD population, a special caution and adequate counseling on the possibility of pathological sleepiness while driving should be done before the initiation of treatment with DAs.

In addition to the roles of the disease process and medications, it has been postulated that nocturnal sleep deprivation may contribute to EDS. Most PSG studies included PD patients referred to a sleep laboratory with subjective complaints of EDS, and did not find a correlation of polysomnographic measures of nocturnal sleep with daytime sleepiness [52, 54, 84]. The presence of obstructive sleep apnea may contribute to EDS [65], but due to paucity of data no definitive conclusion can be made [73]. Restless legs syndrome (RLS) and PLMD have not been associated with increased daytime sleepiness in the PD population [73, 97]. It is likely that nocturnal sleep deprivation due to sleep disorders confers a susceptibility to EDS that may be enhanced or triggered by use of dopaminergic medications [8].

Evaluation

A detailed medical history with special emphasis on sleep history is an initial step in the evaluation of EDS. Specific inquiry into daytime sleepiness often brings out symptoms that the patient may not recognize as part of the disease, or erroneously associates with the motor symptoms. A collateral history obtained from the spouse/care-giver often provides more objective insight into EDS, since patients may underestimate the degree of their sleepiness. This may be the result of a habituated response on the background of a chronic daytime sleepiness or an amnestic phenomenon [98].

Several objective and subjective diagnostic tools have been used for the diagnosis of EDS in PD patients. The multiple sleep latency test (MSLT) is considered the gold standard for the diagnosis of EDS, and has been used in the PD population [52, 84]. Although the MSLT can quantify the degree of EDS, it is expensive,

time consuming, and, therefore, not practical for screening purposes. Actigraphy is a useful indicator for diurnal activity levels, although it has not been adequately assessed in PD as a measure of sleep–wake cycles [18].

The Epworth Sleepiness Scale (ESS) is a subjective, 8-item questionnaire, widely used for the evaluation of EDS. Although considered to have good psychometric properties and a stable hierarchical item structure for the assessment of EDS in PD, the validity of ESS to adequately quantify EDS remains controversial. Up to 4% of PD patients who report an ESS score >15 do not appreciate daytime somnolence [99].

The Parkinson's Disease Sleep Scale (PDSS) is a recently developed instrument designed to evaluate quality of sleep in PD [100]. This scale has been validated and translated into several European languages. It is a visual analog scale addressing 15 commonly reported symptoms associated with sleep disturbance in PD with a maximal score of 150 (Figure 18.1). The questions address sleep onset and sleep maintenance insomnia, nocturnal motor symptoms, nocturnal restlessness, dystonia, pain, neuropsychiatric symptoms, nocturia, and EDS. The SCOPA-SLEEP is another instrument specifically designed to assess sleep disturbances in the PD population [101]. It consists of two subscales that address daytime sleepiness and night-time sleep, and an additional question that evaluates overall sleep quality on a 7-point scale. The scale correlates well with the Pittsburgh Sleep Quality Index and the ESS [101]. Several other instruments, including the Stanford Sleepiness Scale and the Karolinska Sleepiness Scale, have also been used for the assessment of sleepiness in PD. Their use remains limited since they capture only a current degree of sleepiness, which may vary from one moment to the next.

Treatment

Treatment of EDS in PD is challenging. Patients' education about healthy sleep hygiene is the initial step in the management of EDS. Patients are advised to maintain regular sleep–wake schedules, avoid naps, exercise regularly, and minimize intake of alcohol, caffeine, and nicotine. If there is a suspicion of a co-existent sleep disorder, patients should be referred to a sleep specialist. Detailed review of the medication regimen is essential. Medications with a soporific profile should be minimized/discontinued, and those with activating properties (e.g. selegiline or amantadine) should be given earlier in the day. The dose of dopaminergic medications may need to be reduced, and the class of dopaminergic agents may need to be substituted for a different one (specifically DA). These medication changes may compromise the control of motor symptoms, and therefore the clinician must balance between the adequate control of motor symptoms and EDS. Patients who experience sudden onset sleep/sleep attacks should be advised not to drive until the issue is resolved.

If EDS does not respond to these measures, the use of stimulants and wake-promoting agents should be considered. Stimulant medications, such as dextroamphetamine, metamphetamine, and methylphenidate have been used for the treatment of EDS with variable success. Amphetamines, however, have addictive properties, can cause disruption of nocturnal sleep, as well as adverse cardiovascular events, and therefore are rarely used for the treatment of sleepiness in the PD population.

Modafinil is a novel wake-promoting agent whose mechanism of action is not fully understood. Modafinil has been evaluated in open-label and controlled trials for the treatment of EDS in PD. While some trials demonstrate improvement in daytime somnolence with daily doses of 100–200 mg/day [102, 103], others did not find any beneficial effects [104]. A small, open-label study showed that modafinil may reduce sleep attacks, and therefore allow for titration of dopaminergic agents in PD patients with sleepiness [105]. Modafinil is well tolerated, and does not affect the motor function of PD patients. Side effects are rare, and include insomnia, constipation, dizziness, diarrhea, elevated blood pressure, and hot flashes.

Melatonin, a neurohormone produced by the pineal gland, has been shown to decrease sleep initiation difficulties and night-time activity in older adults. In a recent study of 40 PD patients with disturbed sleep, administration of 50 mg of melatonin daily for 2 weeks resulted in significant improvement in subjective sleep disturbance, sleep quality, and daytime sleepiness [106]. Ramelteon (Rozerem), a hypnotic agent approved for sleep initiation insomnia, which acts as a melatonin receptor agonist, may be beneficial in PD, but no data are available.

Deep brain stimulation (DBS) has become an important treatment option for PD patients with disabling motor complications and dyskinesias. Several authors reported an improvement in nocturnal sleep in PD patients who underwent DBS [107, 108]. The impact of DBS on EDS, however, has not been systematically studied.

How would you rate the following, based on your experience during the past one week? (Place a cross on the appropriate point on the line)	
1. The overall quality of your night's sleep is:	AWFUL — EXCELLENT
2. Do you have difficulty falling asleep each night?	ALWAYS — NEVER
3. Do you have difficulty staying asleep?	ALWAYS — NEVER
4. Do you have restlessness of legs or arms at night or in the evening causing disruption of sleep?	ALWAYS — NEVER
5. Do you fidget in bed?	ALWAYS — NEVER
6. Do you suffer from distressing dreams at night?	ALWAYS — NEVER
7. Do you suffer from distressing hallucinations at night (seeing or hearing things that you are told do not exist)?	ALWAYS — NEVER
8. Do you get up at night to pass urine?	ALWAYS — NEVER
9. Do you have incontinence of urine because you are unable to move due to "off" symptoms?	ALWAYS — NEVER
10. Do you experience numbness or tingling of your arms or legs that wake you from sleep at night?	ALWAYS — NEVER
11. Do you have painful muscle cramps in your arms or legs whilst sleeping at night?	ALWAYS — NEVER
12. Do you wake early in the morning with painful posturing of arms and legs?	ALWAYS — NEVER
13. On waking do you experience tremor?	ALWAYS — NEVER
14. Do you feel tired and sleepy after waking in the morning?	ALWAYS — NEVER
15. Have you unexpectedly fallen asleep during the day?	FREQUENTLY — NEVER

Figure 18.1. The Parkinson's Disease Sleep Scale. Patients are asked to mark their responses according to severity by placing a cross mark on the 10-cm line. The millimeter scale printed on a transparency (not shown) is then applied on the 10-cm lines to measure the response in decimal figures (10 representing the best, and 0 worst score). Adapted from [100].

Future directions

Further research should focus on better understanding of the pathophysiological mechanisms underlying sleep dysfunction and EDS in PD. The role of circadian rhythm disruption in the development of sleep disturbances in PD should be investigated systematically. Prospective studies of the development and natural history of sleep disorders in PD cohorts are needed. The majority of the therapeutic recommendations for sleep disorders in the PD population are

based on open-label small patient cohort clinical trials or case reports. Therefore, double-blind, placebo-controlled clinical trials with a large number of patients are necessary in order to establish the efficacy and safety of therapeutic interventions aimed at the treatment of sleep dysfunction in PD.

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Part 3
Chapter
19

Sleep disorders in the elderly

Sleep and circadian rhythm disturbances in Alzheimer's disease

David G. Harper

Introduction

Alzheimer's disease (AD) is an age-associated neurodegenerative disorder characterized by a progressive loss of neurocognitive function and the emergence of a wide variety of behavioral symptoms. Notable among these behavioral symptoms is the appearance of sleep disturbances that can have a debilitating effect on care-givers and frequently precipitate institutional placement of the patient [1]. These cognitive and behavioral changes are driven by neuropathological changes and degeneration that occurs in the brain in a predictable pattern [2]. While management of sleep disturbance in patients with AD is certainly important for behavioral reasons [3], recent research also suggests that disruption of sleep integrity can interfere with memory consolidation, adding to the cognitive dysfunction in these patients [4]. A significant problem, historically, in studying sleep disturbance in AD has been the lack of consensus guidelines to direct treatment protocols, although recently published guidelines have helped improve this situation dramatically [3].

Regulation, consolidation, and architecture of sleep

In normal adults, sleep is a nocturnal event. Sleep initiation occurs at a relatively predictable time each evening and sleep continues throughout the night with minimal interruption. Some time after dawn, waking from a night of sleep is normally accompanied by a sense of refreshment and vigor. Normal adults can also override this pattern in the face of environmental or other demands and remain awake or fall asleep at times other than the biologically optimal ones. The management of this cyclical change in consciousness, and its volitional perturbation, can best be expressed as the interaction between two opponent processes that can be expressed as mathematical functions [5]. The process we are most familiar with day-to-day is the homeostatic sleep process, which accumulates need to sleep as a function of the total amount of time we have been awake (Figure 19.1). This homeostatic process acts as a modulator of sleep, expressed as a saturating exponential function with the duration of wakefulness increasing sleep pressure and time spent asleep decreasing it.

A separate circadian process, however, plays an additional role by consolidating sleep and wakefulness and temporally locating sleep during the night-time hours. It can be best modeled as a circular function with a period closely approximating 24 hours [6, 7]. The mechanism behind this circadian process or rhythm is via the promotion of alertness during the diurnal period [8]. Then, with the removal or lessening of this alerting influence during the nocturnal period, the homeostatic process can take over and sleep is maintained throughout the night, gradually eliminating the accumulated sleep debt. These two interacting or "opponent" processes yield a highly flexible system that maintains an optimal homeostatic adaptation to the day–night cycle and to environmental demands.

Within sleep, very important changes occur in the electrical activity of the brain and periphery [9, 10]. These changes, detectable by EEG, have been described as a cyclical architecture characterized by oscillations between periods of slow wave activity (stage 3–4) where sleep is deepest and faster activity (stage 2) where arousal occurs more easily. The periods of lighter sleep are interspersed with periods of rapid eye movement (REM) sleep during which brain wave activity is indistinguishable from waking activity, while the musculature enters a state of atonia, the eyes move rapidly, and dreaming occurs [11]. The proportion of time spent in these different brain states shifts over the course of the night with slow wave sleep predominating following initiation of sleep. The proportion of sleep time devoted to stage 2 and REM sleep gradually increases over the course of the night.

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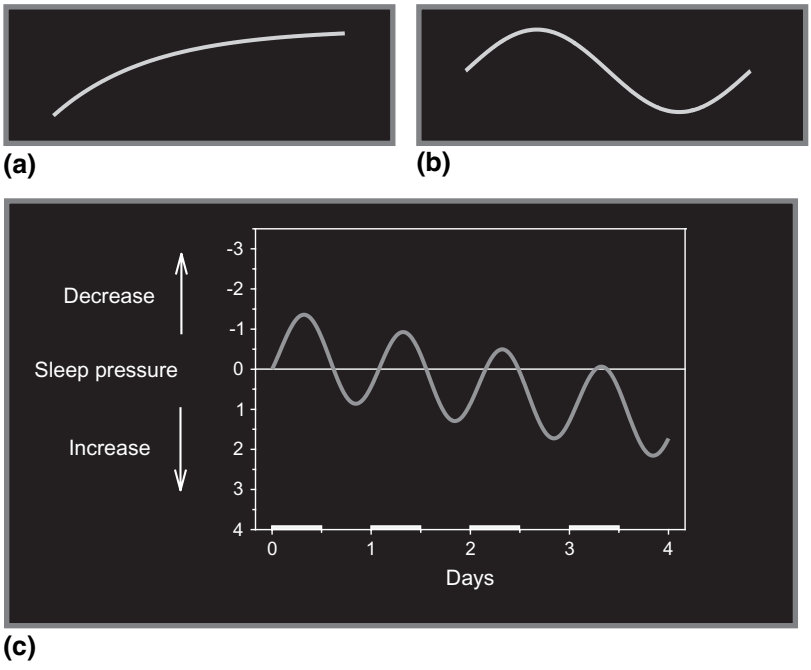

Figure 19.1. Two dynamic processes interact to provide flexible regulation of sleep and wake states. The first process (a) is homeostatic and builds need to sleep as time spent awake increases, whereas the second process (b) is oscillatory and increases wakefulness during the late diurnal period. The independent contributions of these two processes can be observed in a paradigm of enforced wakefulness over several days (c).

These features of sleep and its regulation become very important in understanding the changes in sleep, cognition, and behavior that occur in AD. Sleep, cognition, and behavior have all been observed to change as a consequence of the normal aging process as well as the pathological processes that occur in AD. However, especially in the early stages of AD, it is quite possible that sleep disturbances that are occurring as a result of normal aging also exacerbate the cognitive and behavioral symptoms of AD. Then, as the disease progresses, sleep disturbances associated with the pathological neurodegeneration characteristic of AD emerge, with further behavioral and cognitive consequences.

Sleep – what is it for?

Sleep has a well-known restorative function. When we awaken after a good night's sleep, we feel refreshed and alert. When a full night's sleep is not achievable, various cognitive activities in several domains can become impaired, and these acute cognitive deficits, observed in normal adults, may be especially significant to patients with AD or other forms of chronic cognitive impairment. The importance of sleep in cognitive performance was first observed in the scientific literature in 1896 [12] in a study of sleep deprivation for 90 hours in three subjects. Further observations have since demonstrated that sleep deprivation can lead to a series of microsleeps that significantly impair performance [13]. Sleep restriction or deprivation can have consequences in tasks of arithmetic processing [14], phonemic fluency and vocalization [15], vigilance [16], attention, [17] and, most importantly for patients with AD, memory [18, 19, 20]. Restricting sleep, even to 6 hours/night, has a cumulative effect on cognitive performance [21] over several nights with increasing decrements in performance observed in a dose-dependent fashion [22]. These decrements in performance are state dependent; therefore, when sleep restriction or deprivation is removed performance returns to baseline.

Another state-dependent effect is the misalignment that can occur between the circadian state and sleep and wakefulness. This misalignment occurs quite frequently in our 24-hour culture with night shift work schedules and rapid transmeridian travel. Maintaining a state of wakefulness during the trough of the circadian cycle can have a profound impact on mood and cognition. Circadian misalignment, induced experimentally, increases feelings of depresion [23] while mild sleep deprivation does not. The impact of circadian misalignment on cognition and alertness is significant and independent of similar effects of sleep deprivation [24], such that the impact of these two influences can be modeled successfully [25].

There is another, more subtle effect of sleep, however, on the domain of memory consolidation. Memory formation can be represented quite simply in a model with two stages, acquisition and consolidation [26]. Acquisition occurs during the presentation of the stimulus, but the memory traces formed at this stage are quite susceptible to interference. Consolidation occurs over a longer period of time, during which the memory trace becomes stable and no longer susceptible to interference. Following consolidation, the neural representation of the task as imaged through fMRI is changed and no longer involves many of the structures engaged during trace formation [27].

Memory is also frequently divided into two components, declarative and non-declarative memory [28]. Non-declarative (or implicit) memory is the memory domain associated with the learning of and performing of tasks that do not utilize conscious memory content, also referred to as "knowing how." Declarative (or explicit) memory involves the conscious recollection of facts or events, also referred to as "knowing what" (Figure 19.2). The underlying neural substrates for these systems are located in different parts of the brain with the medial temporal lobe (hippocampus, entorhinal, and perirhinal cortices) being the most important in declarative memory [29]. This mesotemporal region is also where damage from AD first accumulates [2]. Non-declarative memory has a much more diffuse substrate involving multiple distributed brain regions that are generally not located where damage from AD occurs during the disease's early to middle stages. It is not surprising, therefore, that patients with AD show intact non-declarative learning even while declarative memory becomes quite impaired [30].

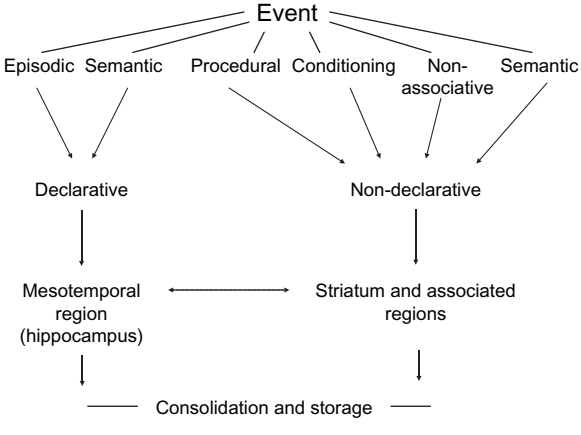

Figure 19.2. Conceptualization of memory is generally organized dichotomously by the type of learning involved (declarative vs. non-declarative) and by the neural substrate where initial encoding of the information occurs. Sometimes both encoding areas are involved. Memory consolidation then involves the long-term transfer and storage of information in diffuse sites separate from the region where initial encoding occurs. Adapted from [32].

The impact of sleep restriction on the consolidation of non-declarative memory is well established [4]. Late night sleep, rich in the REM state, appears to be particularly important for the consolidation of non-declarative memory from studies of both late night sleep deprivation and polysomnographic changes in REM following non-declarative learning. However, there is not likely to be much interaction between sleep loss and AD in non-declarative memory since the brain regions responsible for acquisition and consolidation remain relatively intact late into the illness.

By contrast, evidence for a role of sleep in the consolidation of declarative memory, though not without controversy [31], has become quite compelling over the last few years. Strong evidence suggests that delta sleep [32] serves a role in declarative memory consolidation. Convincing data also implicate sleep spindles, relatively high-frequency (14–16 Hz) bursts, common during stage 2 sleep [33, 34, 35], in the consolidation of declarative memory. Work in animal models suggests an underlying mechanism for this process. Hippocampal "ripples," short (30–200 ms) bursts of high-frequency (~200 Hz) CA1 activity, selectively reactivate (i.e. fire in the same pattern as during memory acquisition while awake) during sleep [36, 37]. In addition, these replays are tightly coupled with the appearance of sleep spindles in the neocortex [38]. These findings imply transfer of hippocampally stored information (memory traces) to cortical regions for long-term storage. The interactive impact of AD and sleep spindles on the consolidation of declarative memory has recently been confirmed [39].

Cognitive impact of Alzheimer's disease

Alzheimer's disease is a debilitating, progressive neurodegenerative disorder. It is clinically characterized by a steady and progressive loss of neurocognitive and functional abilities. Patients diagnosed with AD frequently also have profound behavioral changes including increases in agitation, depression, apathy, anxiety, and many other troubling symptoms. Initially, complaints can be mild and involve difficulty encoding new declarative memories. These early deficits, comprising

a prodromal syndrome that frequently, with the passage of time, leads to a diagnosis of AD, do not generally interfere with activities of daily living but can lead to some curtailment of tasks requiring intense cognitive activity. Impairment of declarative memory and the learning of new information gradually increase as the neurodegenerative syndrome progresses. This initial impairment can be accompanied by deficits in frontal executive functioning and visuoconstructional impairments that are characterized by a developing inability to plan and organize. When these deficits begin to interfere with the patient's functional abilities the diagnosis of AD can be made.

Gradually, the number of cognitive domains that are affected by AD increases as the disease progresses from the mild to the moderate stage. Semantic and phonemic fluency become degraded, spatial disorientation increases and ideomotor sequences become impaired leading to a much greater loss of functional abilities. Recognition of familiar people or places also becomes difficult and occasional false recognition leads to increasing confusion and loss of orientation. Behavioral symptoms increase and become more and more disruptive to patients and those helping to care for them. Therefore, given the impact that sleep loss can have on memory consolidation and other cognitive and behavioral domains in normal adults, the consequences to a patient with AD is likely to be quite profound.

Sleep and circadian changes in AD

Sleep disturbances in AD have been noted using a variety of subjective and objective measures, and these sleep disturbances increase with the severity of dementia [40, 41, 42, 43]. In general, it is quite likely that loss of sleep in AD has an impact on global cognitive ability in these already vulnerable patients. However, another troubling possibility is the potential for particular sleep stages or features of sleep to become less prominent over the course of the illness, which could then have a disproportionate effect on memory consolidation. For evidence in this area we can look at the polysomnographic changes that have been observed in AD patients.

Polysomnographic studies

Changes in sleep architecture in AD were first mapped over 30 years ago. These changes are, of course, confounded with the alterations in sleep that are a consequence of normal aging. The majority of sleep architecture changes occurring in AD therefore are simply an exaggeration of those seen in a cognitively normal but aged population. However, there are some prominent differences between these two groups, and these are likely due to the specific neurodegenerative pattern seen in AD [2].

Findings from initial studies demonstrated that the changes in NREM sleep architecture in AD are similar to, but more extreme than, those seen in normal aging [44, 45, 46, 47], including, most prominently, a reduction in slow wave sleep that was greater than that seen in a normal elderly population. However, a notable exception to the similarity between aging and AD was the reduction in sleep spindles seen in AD populations that was not seen in normal elderly when compared to younger adult populations [46, 47].

Expression of REM sleep, however, follows a different path from normal aging in patients with AD. Rapid eye movement latency in particular, while shorter in duration in an aging population compared to younger adults, is longer in AD than in aged controls [48]. Alzheimer's disease patients also show a shorter mean duration of REM periods than normal controls. This is likely due to the degeneration seen in cholinergic neurons in early AD. In contrast, measures of REM intensity and also the number of REM periods during the night do not appear to change with the onset of mild to moderate AD, although in severe AD there may be changes that have not, as yet, been observed due to the difficulties associated with the use of polysomnography in this population. The changes in REM sleep seen in AD were severity specific [49] with patients with mild AD showing few changes but those with moderate to severe AD becoming quite different from normal controls.

Another source of sleep disturbance in AD is the increased prevalence of sleep disordered breathing (SDB) in advanced dementia [50]. The prevalence in this population has been estimated to be between 35% and 63% [51, 52, 53], whereas prevalence in a normal geriatric population generally ranges between 20% and 25% [54]. The estimated prevalence increases with advancing dementia [51] limiting stage 3 and stage 4 sleep beyond that seen in dementia patients of similar severity who do not have sleep disordered breathing [55].

Activity and circadian studies

Measuring sleep with polysomnography, however, in patients with even mild to moderate AD can be quite

difficult. And, as dementia severity worsens, the ability of patients to co-operate with a polysomnography protocol can become quite limited. The presence of behavioral disturbances, the profound memory loss, and disorientation all combine to present a formidable challenge to the technologist in getting high-quality data. Also, in many studies the primary endpoint is the quantity of sleep, and information on sleep stages and breathing is superfluous. Therefore, one strategy that has been employed to quantify sleep–wake behavior has been to make use of the high correlation between locomotor activity levels and the sleep–wake state [56] by using wrist-worn activity monitors. Actigraphy, in addition to providing information about the sleep–wake state of patients, can also be used to provide a limited estimation of circadian performance in patients with AD. They are relatively non-intrusive, compared to polysomnography, and provide an unbiased measure of movement that is particularly useful in characterizing both sleep–wake and the phase and strength of the circadian rhythm in these patients.

This last point, the circadian rhythm, has some controversy associated with its measurement by actigraphy, especially regarding how to quantify it in data that are masked by the many components of volitional activity and external schedules. Data derived from actigraphy are not continuous and do not, prima facie, meet the assumptions for the parametric models that are usually used in the analysis of circadian rhythms derived from time-series data. The conclusion from this line of thought is that motor activity is a poor substitute for the more traditional methods of measuring the strength and phase position of circadian rhythms in humans such as the constant routine [57, 58, 59], the forced desynchrony protocol, and the dim-light melatonin onset (DLMO) [60].

However, Alzheimer patients, in general, are not appropriate for study with constant routines and especially forced desynchrony protocols due to the rigors associated with these procedures. In addition, measuring circadian phase with the DLMO is not possible in these patients due to the loss of circadian and nocturnal melatonin secretion [61, 62].

Therefore, it has been important to develop non-parametric methods that can indicate the strength of the underlying circadian rhythms from activity data derived from AD patients. The two most commonly used methods involve the interdaily stability (IS) and intradaily variability (IV) statistics [63]. The IS measures the stability of the rhythm from day-to-day. So, for example, a patient with a high IS would have activity that is very similar at the same hour of each day and, by inference, would be expressing a stronger circadian rhythm than a patient with a low IS, who would show chaotic activity without much consistency from day-to-day. Intradaily variability conversely measures the hour-to-hour variability of activity. A high IV therefore suggests a great deal of fragmentation in the activity pattern with less consolidation of sleep and wakefulness (Figure 19.3).

Evidence for the disruption of the circadian rhythm in AD, based on non-parametric analysis, is well established and remarkably consistent across study sites. Interdaily stability was significantly lowered in patients with moderate to severe AD although not in patients with mild AD [41, 64, 65, 66]. Interdaily stability was also shown to be closely correlated with cognitive decline [67] in a sample of demented elderly women. Intradaily variability in patients with AD, while trending towards increase, has not been as clearly affected across the severity spectrum of AD [65, 68], although this may be due to the presence of other dementia diagnoses in the sample of AD patients [42, 68]. These results suggest that the circadian rhythm is disturbed in AD, but do not provide information on how to best target intervention. Therefore, information on phase disturbance, which these non-parametric analyses do not provide, becomes very important to establish in order to guide therapeutic intervention.

Evidence of phase disturbance of the circadian rhythm in patients with AD comes from many different studies using a variety of methods. Parametric circadian methods, such as cosinor analysis, have been used to examine time-series activity recordings in AD patients for clues about changes in circadian phase specific to AD. In general, these analyses of activity have indicated a phase delay of the activity rhythm [42, 64, 68, 69, 70]. However, activity phase delays cannot be considered conclusive evidence of a change of phase of the circadian oscillator in AD.

Core body temperature studies have also been carried out in patients with AD. Core body temperature has the advantage of being tightly coupled to the output of the circadian oscillator located in the suprachiasmatic nucleus of the hypothalamus [71, 72]. However, core body temperature also can be affected by influences not associated with the endogenous circadian rhythm. These influences include volitional activity, feeding

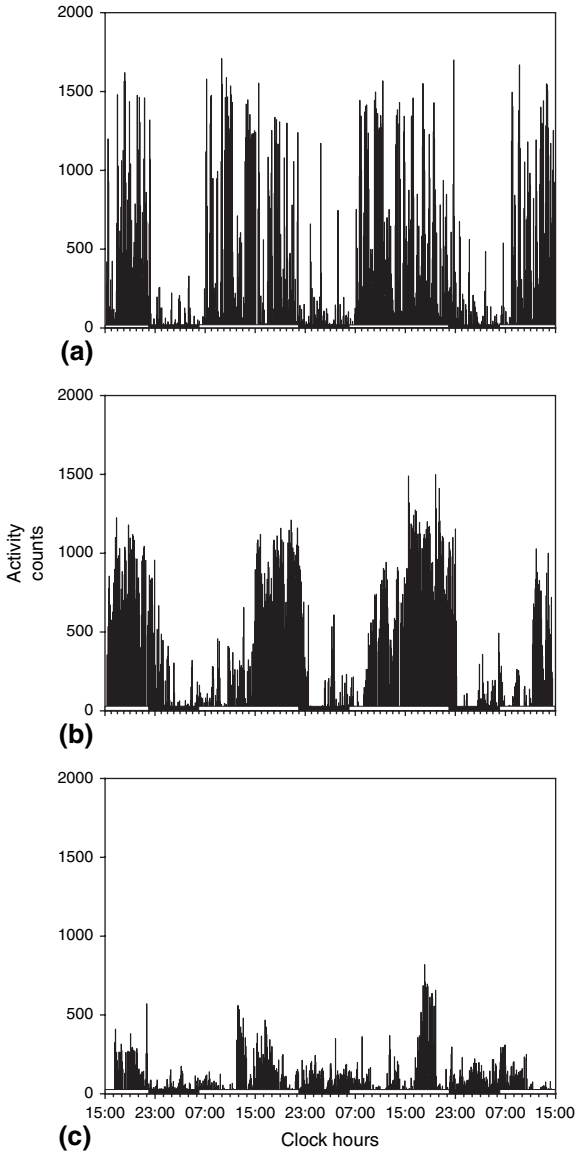

Figure 19.3. Time-series activity recordings from an elderly control subject (a), from a dementia subject (Alzheimer's disease) with consolidated activity but delayed phase (b), and from a dementia subject (dementia with Lewy bodies and Alzheimer's disease) showing a highly fragmented pattern of activity (c). Adapted from [42].

and meal schedules, exposure to environmental light, sleep, and many others. Therefore, the more of these "masking" influences that can be removed the better the estimate of circadian phase and amplitude. Clearly, with AD patients, removing masking influences is difficult. Therefore, studies have been made of core body temperature in AD patients without removing masking influences. These studies also show a significant phase delay in the core body temperature rhythm [64] that is highly specific to AD [68] and more profound with increasing severity of illness [41, 42].

However, as noted above, these studies can only give a rough estimate of the circadian phase in patients with AD. There has been one study performed using full unmasking, constant routine conditions to estimate the endogenous circadian phase and endogenous circadian amplitude in AD patients [73]. In this study, seven males patients with AD (five of seven with pathologically confirmed AD) were compared to seven normal elderly males and seven young control males (Figure 19.4). This study confirmed the presence of a weakened endogenous circadian rhythm amplitude and profoundly delayed phase in AD patients. Indeed, estimates of the endogenous circadian phase were much later in this study than in previous studies of core body temperature phase in AD patients suggesting that environmental influences were biasing the circadian estimations of the prior studies towards understating the amount of phase disturbance in AD.

Another source of evidence for phase delay of the circadian rhythm in AD comes from multiple sleep latency test (MSLT) data [74]. Multiple sleep latency tests show an AD severity specific shortening of sleep latency, especially in the morning hours [75]. These results are consistent with a delay in circadian phase occurring as a consequence of AD. Taken together, these findings from studies of the endogenous circadian rhythm by use of a constant routine and the MSLT of a delayed circadian phase are strongly suggestive of an AD severity-dependent impact on the circadian rhythm.

Circadian treatment of sleep and AD symptoms

Given the well-established deterioration in sleep seen in patients with AD, and the evidence that the circadian rhythm of AD patients has lost environmental entrainment, there are likely to be several deficits that accrue in these patients. The first is the effect of loss of total sleep on the several domains of cognition and mood described previously. The second is the impact of the loss of specific sleep stages and features such as sleep spindles on memory consolidation. The third is the impact of circadian misalignment on cognitive performance and mood. Clearly these discrete problems are interacting as well leading to a condition where cognition and behavior, already degraded by

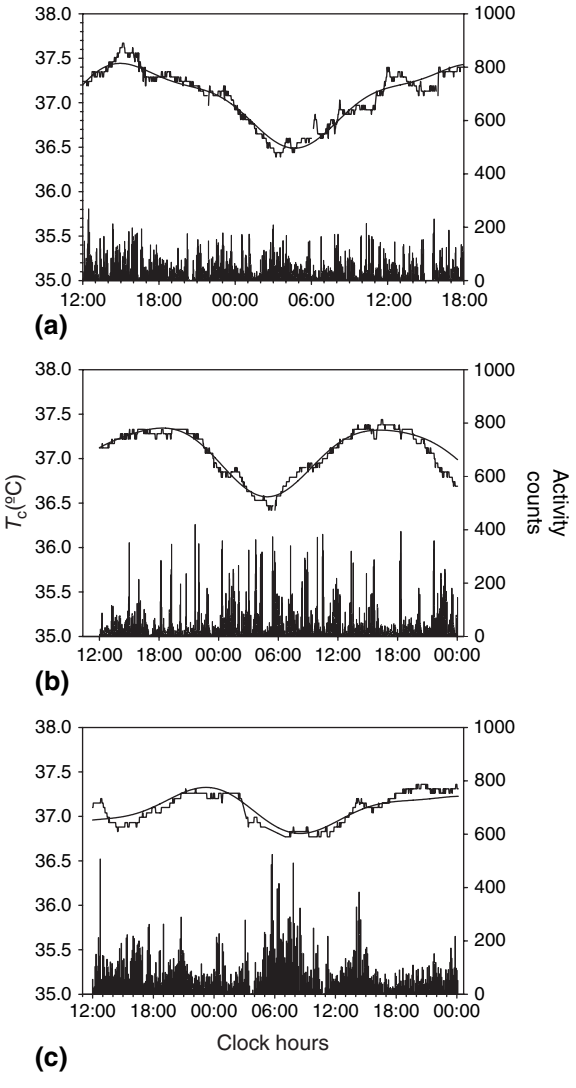

Figure 19.4. Core body temperature recordings from three subjects taken under "unmasking" or constant routine conditions (blue) with a 2 harmonic function fit to the temperature data (red). Activity is shown (black) to demonstrate the wakefulness over the constant routine period. (a) A normal young adult subject shows a robust amplitude core-body temperature rhythm under these conditions with a cycle nadir around 05:00 (derived from the 2 harmonic cosinor model). (b) An elderly subject with no signs of dementia shows a reduced amplitude but normal phasing with a nadir around 05:00. Frequently, normal elderly subjects show phase positions that are slightly earlier than young adults, although that is not the case in this subject. (c) A subject with Alzheimer's disease shows, in addition to reduced amplitude, a prominent phase delay typical in more than half the subjects with advanced disease. Adapted from [73].

AD, is further inhibited by sleep and circadian disturbances.

Given these particular areas of disturbance in patients with AD, one promising option would be the use of chronotherapeutics, such as bright light and/or melatonin in an attempt to treat the underlying chronobiological disturbance in these patients. The strategy would be to bring the circadian rhythm into environmental entrainment and thereby improve first sleep and then mood and possibly cognition. Two agents, melatonin and phototherapy (light treatment), have received substantial testing in AD populations both alone and in combination, with results that show some degree of efficacy. There are, however, several barriers to the delivery of effective treatment of sleep and chronobiological disturbances of AD using light and melatonin.

Light has come into common usage for the treatment of seasonal affective disorder, and the standard mode of delivery is a light box delivering up to 10 000 lux in the angle of gaze. The use of this particular intervention strategy in Alzheimer patients, however, can be somewhat more difficult to achieve due to their inability to understand and co-operate with the treatment. To ask an Alzheimer patient, particularly one with advanced dementia or significant agitation, to sit and gaze in the general direction of a light box for a significant period of time is really not practical. Also, since the endogenous circadian phase of patients with moderate to severe AD has been shown to be significantly delayed in AD patients, the timing of the treatment, with either light or melatonin, becomes a significant issue [73].

Early trials of chronotherapeutics in patients with AD used a variety of different methods to overcome these difficulties. These were generally open-label or naturalistic studies of the effect of light in patients with dementia. Two naturalistic studies first demonstrated that patients with mild [76] and moderate to severe [69] dementia received less light than cognitively intact individuals living under conditions similar to the dementia patients. Light therapy using light boxes was also the subject of a number of open-label trials in the 1990s. One of the first light treatment trials in patients with probable AD used light of 1500–2000 lux, delivered in the evening, to measure nurse-rated sleep and disruptive behavior (sundowning). Both measures were reported to improve with this treatment. Morning bright light therapy (3000–3500 lux for 2 hours) was also found to improve sleep measures in patients with dementia [77]; however, when a randomized, placebo-controlled cross-over design was used in a later study this effect was found to be restricted to those patients with a

non-Alzheimer dementia [78]. Another approach that showed promise was the use of a light therapy room where full spectrum lights were installed and the patients essentially self-administered light during the day at an intensity of approximately 1100 lux (790–2100 lux) in the angle of gaze. This type of delivery was found to be efficacious in open-label trials, improving the rest–activity rhythm of patients significantly [79].

Double-blind, placebo-controlled trials of light therapy are difficult to perform logistically. It is usually fairly trivial to present a placebo to patients, caregivers, and clinical staff that is indistinguishable from the active treatment in most medication trials. In light treatment trials, however, it is difficult to present an inactive treatment that cannot easily be differentiated from the active treatment by everyone involved in the study. Therefore, placebo-controlled studies of light treatment for sleep and circadian disturbance should not be considered blind or double-blind and need to be interpreted with this difficulty in mind.

Recent trials of light treatment with a placebo control have looked at several endpoints including the rest–activity rhythm [80, 81, 82], depressive symptomatology [83], and behavioral symptoms [84, 85] in patients with advanced dementia. These trials generally include morning light compared to afternoon light and increased environmental light as well as other light conditions in cross-over designs. In trials where the rest–activity rhythm was the primary outcome measure, it was observed that increasing environmetal light showed efficacy in promoting stability of circadian phase [81], consolidating sleep and wakefulness [80], and increasing night-time sleep [82]. However, results are also inconsistent with studies not showing statistically significant improvements in similar domains even though the overall trends in the data are highly suggestive of general improvement in the rest–activity rhythm, especially with morning or general daytime light. There is also some inconsistency in studies where agitation is the behavioral endpoint with one study showing inconsistent effects [84] and one showing amelioration of agitation [85]. Finally, much as has been observed with seasonal affective disorder (SAD), morning bright light was found to improve depressive symptomatology in institutionalized patients with dementia [83].

The inconsistent but generally positive results from these trials offer encouraging evidence that chronotherapeutical intervention in patients with moderate–severe dementia could be useful for these patients. The inconsistencies in results between studies, however, are somewhat troubling and make interpretation more difficult. Several factors could be impinging on the clarity of results in these trials. The first, as previously mentioned, is that the difficulty with lack of blinding in these trials could be impacting the subjective ratings. However, the more significant issue is that many of these trials present light based on external clock time rather than the subjective circadian time of the patient, which can be quite different from clock time [73]. This could lead to a situation where, for example, morning light causes circadian shifts in a subgroup of patients that move their circadian phase further out of alignment with the environment leading to a worsening of their symptoms. One approach to ameliorating this problem is to allow light treatment trials to focus on a paradigm of self-administration where light is available to the patients in a specific location during the daytime [79]. Patients can then avail themselves of the opportunity for exposure to bright light when they are in their naturally active phase and not lead to exposure when the patient is not as active during their circadian trough. This would likely shift those patients who are out of phase with the environment to a more normal phase without presenting as much danger of causing phase shifts away from the environment.

Early open-label studies of melatonin were equivocal although some showed promise in treating both behavioral and sleep disturbances in AD [86, 87]. Evening melatonin was also shown to be efficacious in a small, placebo-controlled, double-blind study for improving night-time sleep and cognitive and non-cognitive symptoms of AD [88]. In a large, multicenter, double-blind, placebo-controlled trial of melatonin at 2.5 and 10 mg 1 hour before sleep for the treatment of insomnia in patients with AD, no significant effects were seen on the objective measures of sleep. However, trends were observed towards sleep improvement with melatonin at both dosage levels, and subjective ratings by care-givers also showed improvement of sleep. No differences between active and placebo groups were observed in adverse event reporting [89].

More recently, two promising clinical trials have moved to a combination therapy employing both melatonin and light. The first, employing morning light and evening melatonin while not showing any significant differences in night-time sleep, showed significant reductions in daytime sleep, improved diurnal activity, and more consolidated circadian activity

[90]. A second study, employing a light self-administration design coupled with 2.5 mg evening melatonin or placebo, showed significant improvements in a large number of domains including cognitive performance, behavioral symptoms, and sleep–wake symptoms with this combination treatment [91]. The combination therapy was clearly superior to either treatment given alone and produced improvements in cognitive symptoms to a similar extent as observed with FDA-approved cholinesterase inhibitors.

The improvements shown in the combination therapy studies suggest that this dual approach may be a most promising intervention strategy in facilities specializing in the care of the elderly with moderately to severely demented patients. The approach of self-administration used in the latter study also lessens the risk of light being given to patients at inappropriate times of day for their subjective circadian phase. While it may seem somewhat surprising at first glance to see improved cognition in patients with dementia in a trial of chronotherapeutic agents directed towards improving sleep and circadian regulation, it actually is quite reasonable to expect improvements in the cognitive domains in these patients based on the effects of sleep restriction or circadian dysregulation on cognition in normal controls. This promising therapeutic effect needs to be replicated, and cognitive endpoints should be added to chronotherapeutic trials in patients with dementia.

Treatment of sleep disordered breathing in patients with dementia

Most treatments for SDB, whose source is suspected to be obstruction of the airway during sleep, involve non-pharmacological interventions intended to physically improve the passage of oxygen through the airway thereby improving blood oxygenation and continuity of sleep. The first-line treatment of choice is usually a continuous positive airway pressure device (CPAP), which splints the airway by delivering an uninterrupted flow of air allowing unobstructed breathing. Clearly, compliance with treatment would be a major concern in patients with dementia, particularly moderate to severe dementia.

A recent study, however, demonstrated that treatment compliance with CPAP could be achieved in patients with possible or probable AD (MMSE mean 25; range 18–30) [92]. In a placebo-controlled, randomized trial comparing active versus sham CPAP in patients with mild to moderate AD, daytime sleepiness was reduced in the active CPAP group and acute improvements were noted in verbal learning (Hopkins Verbal Learning Test) and executive functioning (Trials B) [93]. The trial mentioned above only examined acute effects (3 and 6 weeks of treatment) and did not look at the chronic impact of improving blood oxygenation on disease progression, which would be a significant endpoint to measure.

Effects on sleep of pharmacological treatment of cognitive symptoms in AD

Literature on the effects of sleep in patients with dementia treated with the two primary drugs approved for treatment of AD is quite sparse, although evidence exists that these treatments may have an effect on different components of sleep. Rivastigmine, a cholinesterase inhibitor, has been observed to extend REM in healthy elderly patients [94]. The first drug approved by the FDA for the treatment of AD, donepezil, is a cholinesterase inhibitor affecting the metabolism of acetylcholine rendering it present in cholinergic synapses for longer periods of time and amplifying cholinergic signaling. However, acetylcholine also has known effects on sleep architecture in the regulation of REM sleep [95]. In a clinical trial of 12 patients with probable AD, donepezil was observed to significantly increase the amount of REM sleep, especially in those patients who benefited cognitively from the drug [96]. A second double-blind, placebo-controlled trial (N = 23) was conducted and it was found that, in addition to an increase in REM sleep measures, there was a significant reduction in the apnea–hypopnea index (AHI) in patients with SDB characterized by an AHI ≥5 [97].

An examination of clinical trial information for galantamine indicated that it increases REM sleep as there was a significant increase in the incidence of nightmares in the group treated with galantamine 24 mg compared to placebo [98]. However, in one large study examining the effect of cholinesterase use on sleep architecture, no differences in the effect on REM sleep were found between placebo and any of the cholinesterase inhibitors studied [99]. Differences were seen between the donepezil versus no cholinesterase inhibitor group in stage 2 sleep with donepezil use being associated with a larger percentage of time spent in stage 2 sleep.

More recently, the glutamatergic NMDA antagonist memantine was approved by the FDA for the treatment of moderate to severe AD. An early randomized, single-blind clinical trial of memantine in severe dementia showed some improvement in sleep variables [100], however, to our knowledge, no randomized or blinded trial has been performed since looking at sleep in AD patients given memantine in a systematic fashion. One case report described the development of psychotic symptoms in a patient taking memantine [101], with intense dreams and difficulty distinguishing dreams from reality. These symptoms resolved following discontinuation of memantine.

Conclusions

Sleep disturbances, far from being an ancillary symptom of AD, may have a far-reaching impact on the course of the illness. Cognitive, behavioral, and caregiver burden are all affected with important consequences. Further research is needed on the actual cognitive burden imposed by sleep loss in AD and mild cognitive impairment.

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Part 3
Chapter
20

Sleep disorders in the elderly

Narcolepsy in the elderly

Michel Billiard

Introduction

Narcolepsy is a disabling sleep disorder characterized by excessive daytime sleepiness and sleep attacks, abnormal rapid eye movement (REM) sleep manifestations including cataplexy (a sudden loss of muscle tone triggered by strong emotions), sleep onset and/or sleep offset paralysis and hallucinations, and disturbed nocturnal sleep. Polysomnographically, narcoleptic patients tend to enter directly into REM sleep. The second edition of the *International Classification of Sleep Disorders* (ICSD-2) distinguishes three forms of narcolepsy: narcolepsy with cataplexy, narcolepsy without cataplexy, and narcolepsy due to a medical condition [1]. The pathophysiology of narcolepsy with cataplexy is linked to the positivity of the human leukocyte antigen (HLA) DQB1*0602 and to the early loss of neurons in the hypothalamus that produce hypocretin, a wakefulness-associated neurotransmitter present in the cerebrospinal fluid. The cause of neural loss could be autoimmune.

The age of onset varies from early childhood to the fifties with a large peak around puberty and a smaller one between 35 and 40 [2]. As such, narcolepsy can be considered a disease of the young. It is, however, a lifelong condition and thus it is of definite interest to consider how it evolves with age. Several studies have concentrated on the evolution of the symptoms of narcolepsy in elderly narcoleptic subjects [3, 4, 5, 6, 7, 8] while others have focused on the polysomnographic and multiple sleep latency features of elderly narcoleptic subjects [5, 11].

In this chapter we will review clinical and polysomnographic features of elderly narcoleptic subjects, and consider co-morbidity and therapeutic issues.

Age of onset and age of diagnosis

The latest age of onset of narcolepsy has not drawn much interest. In a review of the records of 106 narcolepsy patients randomly chosen from more than 700 records, the latest age of onset of excessive daytime sleepiness was 54 in men and 56 in women, and the latest age of onset of cataplexy was 57 in men and 61 in women [7]. Circumstances of onset were not specified. In a later study by Ohayon *et al.*, including 157 patients, the latest appearance of excessive daytime sleepiness was in a patient older than 60, while the latest appearance of cataplexy was in four patients older than 60 [8].

There is evidence that a considerable variance exists between the appearance of symptoms in narcoleptic patients and the time at which they are actually diagnosed. A number of narcoleptic patients are older than 40 at diagnosis, this being due either to mild disease severity or misdiagnosis, or diagnosis delayed until late-life expression of cataplexy, or narcolepsy lacking cataplexy [9]. Worth mentioning is that a substantial population of patients goes through life undiagnosed [10].

Time sequence of symptoms

Temporal succession of the two major symptoms of narcolepsy with cataplexy depends on the age of onset. The succession of symptoms after early onset of excessive daytime sleepiness is characterized by a long latency between excessive daytime sleepiness and cataplexy. The period of latency, however, is attenuated if there is a late onset of excessive daytime sleepiness [7]. In narcoleptic patients aged 60 years or older, cataplexy is more likely to occur before excessive daytime sleepiness [8].

Clinical features

According to the study referred to above [8] there is no significant change in sleepiness with age among narcoleptics on the Epworth sleepiness scale and on the severity assessment of daytime sleepiness. Qualifying this overall finding, however, is further evidence that considerable variance exists in symptom onset and in

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patients' adjustment to their condition. In a study evaluating the outcome of daytime sleepiness in 70 narcoleptic patients with symptoms of cataplexy, 30 patients reported a steady, disabling condition, 18 mentioned a rather satisfactory adaptation to their condition, usually after years of difficulties, 12 indicated a tendency to worsening of excessive daytime sleepiness, either gradual or abrupt following a special circumstance, while the outcome of excessive daytime sleepiness could not be validly assumed in the last 10 patients due to a clinical course of less than 10 years [4].

As far as cataplexy is concerned, Ohayon *et al.* did not find any difference in terms of frequency of the episodes in their young and old narcoleptic patients [8], while Dauvilliers *et al.* found a trend in favor of a progressive decrease in the frequency of cataplexy with age [11].

Apart from the severity of excessive daytime sleepiness and the frequency of cataplexy with age, a special issue is the eventual outcome of both symptoms. Ohta *et al.* carried out a 10- to 21-year follow-up study in 101 narcoleptic patients and found an absence of excessive daytime sleepiness at the time of the survey in 11 patients (10.9%) without medication [3]. Other authors have been less optimistic. Roth estimated that 88% of cases had a steady course and 12% had remissions and exacerbations [12], Parkes mentioned short remissions lasting 1–6 months [13], and Billiard *et al.* did not notice a single case of disappearance of symptoms in their series of 70 patients [4].

On the other hand, most investigations report that cataplexy symptoms spontaneously disappear with advancing age in some patients. The proportion of patients exhibiting this has been recorded as 10–20% [13], 15.7% [4], and 20.8% [3]. This is even more the case with hypnagogic hallucination and sleep paralysis, vanishing in 36.9% and 35.4% of patients, respectively [4].

Polysomnographic and multiple sleep latency test features

Lamphere *et al.* reviewed the charts of 228 adult patients given the diagnosis of narcolepsy and compared the results of polysomnography and the multiple sleep latency test (MSLT) in 17 narcoleptic patients aged 20–29, 64 aged 30–39, 80 aged 40–49, 42 aged 50–59, and 25 aged 60 and over [5]. The results of the ANOVA clearly revealed an increase in disturbed nocturnal sleep as a function of age. Total sleep time and sleep efficiency significantly decreased, and wake after sleep onset, number of awakenings, and percentage of NREM sleep stage 1 significantly increased across the decades. On the contrary, the results of the MSLT displayed no significant age-related effects in terms of daytime sleepiness, with the mean latency to sleep onset and the frequency of sleep onset REM periods (SOREMPs) not differing in the various age groups. This is in accordance with the notion that night sleep does not predict day sleep in narcoleptic patients [14].

More recently, Dauvilliers *et al.* reviewed the charts of 383 well-defined narcolepsy with cataplexy patients (236 from Montpellier, France, and 147 from Montreal, Canada), grouped as patients aged less than 21 years (58), aged 21–35 years (65), aged 36–50 years (127), aged 51–65 years (101), and aged over 65 years (32) [9]. This study showed an unequivocally progressive increase in the mean sleep latency on the MSLT and a progressive decrease in the number of sleep onset REM periods as a function of age.

Co-morbidity

Knowledge about the co-morbid disorders in narcolepsy is important inasmuch as it may sometimes contribute to diagnosis and it may also bring some insights into the pathophysiology of narcolepsy. Interest in co-morbidity has been mainly highlighted by a German group [15, 16]. Among the most frequently associated diseases (>10% of patients) were parasomnias (sleep walking, sleep talking, nightmares, REM sleep behavior disorder, and bruxism), sleep-related breathing disorders (obstructive sleep apnea syndrome, OSAS), sleep-related movement disorders (periodic limb movement disorder, PLMD), internistic diseases (obesity), neurological disorders (headache), and psychiatric disorders (depression). Of most concern in elderly narcoleptic patients are REM sleep behavior disorder and the frequently associated olfactory dysfunction, OSAS, and PLMD.

REM sleep behavior disorder (RBD)

RBD is a form of motor dyscontrol due either to loss of REM sleep-related muscle atonia or excessive locomotor drive or both. It is characterized by complex, vigorous, and frequently violent dream-enacting behavior during REM sleep [1]. It can result in injury, most commonly to the partner as opposed to the patient him- or herself. Patients are most frequently older males. RBD may occur alone ("idiopathic RBD") or be associated with neurodegenerative diseases within the synucleinopathy spectrum, Parkinson's disease, dementia with Lewy bodies and multisystem atrophy, or narcolepsy. In uncontrolled studies the frequency of RBD in narcolepsy has

been estimated to be 7% [17], 19.9% [18], or 36% [19]. In a recent controlled study comparing 16 patients with narcolepsy with cataplexy, 16 "idiopathic RBD," and 16 normal controls, higher percentages of REM sleep without atonia, phasic electromyographic activity, and REM density were found in patients with narcolepsy with cataplexy than in normal controls [20]. By contrast, patients with idiopathic RBD had a higher percentage of REM sleep without atonia but a lower REM density than patients with narcolepsy or normal controls. Interestingly in this sample, no significant behavioral manifestations in REM sleep were noted in narcoleptic patients, possibly due to the unavailability for further analysis of video recordings previously performed in the sleep laboratory.

Olfactory dysfunction

The majority of patients with idiopathic RBD present with hyposmia [21, 22], a sign of possible later development of parkinsonism. Yet, not only patients with idiopathic RBD, but also patients in whom RBD is associated with narcolepsy, present with a marked olfactory dysfunction characterized by an increased olfactory threshold and an impaired odor discrimination and identification [21]. Studying olfactory function in 20 narcoleptic patients with and without associated RBD, Stiasny-Kolster *et al.* could show that narcolepsy per se is associated with olfactory dysfunction, but that in contrast to patients with idiopathic RBD, hyposmia in patients with RBD associated with narcolepsy is unlikely to be a predictor of developing parkinsonism [23]. Given the presence of both hypocretins and their receptors in the rat olfactory system [24], it would be of the utmost interest to study whether this olfactory dysfunction comes from a degeneration of the neurons of the nasal mucosa in narcoleptic patients

Obstructive sleep apnea syndrome

The frequency of sleep-related breathing disorders in narcoleptic patients, 16%, is much higher than the 4% given for a control population [16]. However the increased frequency is not due to age, but rather to obesity, which is especially frequent in children with narcolepsy.

Periodic leg movements during sleep (PLMS)

According to a recent study measuring the frequency of PLMS during NREM sleep and REM sleep in narcoleptic patients and in normal controls, and assessing the impact of PLMS on nocturnal sleep and daytime alertness, more narcoleptics than controls had a PLMS index greater than 5 per hour of sleep (67% versus 37%) and greater than 10 (53% versus 21%) [25]. A significant increase of PLMS index was found with aging in both narcoleptic patients and controls. Patients with an elevated index of PLMS had a higher percentage of stage 1 NREM sleep, a lower percentage of REM sleep, and a shorter mean sleep latency on the multiple sleep latency test.

Narcolepsy as a protection against neurodegenerative diseases?

According to the literature and clinical experience, narcolepsy is not associated with neurodegenerative diseases including neither movement disorders nor primary degenerative dementias. This is all the more remarkable inasmuch as rapid eye movement disorder and olfactory dysfunction, well-known predictors of parkinsonism in normal subjects, are frequent features of narcolepsy. There is no evidence, however, that narcoleptic patients with rapid eye movement disorder ever develop parkinsonism. This observation suggests a hypothesis that narcoleptic symptoms may represent a possible protective mechanism against neurodegenerative disorders

Treatment

We are not aware of any studies dealing with the treatment of elderly narcoleptic patients. Moreover, various drugs, such as stimulants, antidepressants, and sodium oxybate used in narcolepsy have been tested in adult patients over a range of ages, but not specifically in elderly subjects. Thus, up to this time, the standard pharmacological treatment of narcolepsy in elderly patients does not differ from that used in younger adults, except in the case of hepatic or renal failure. On the other hand, the implementation of a behavioral management of excessive daytime sleepiness and sleep attacks may be easier to propose to elderly narcoleptic patients due to the greater flexibility of their daily schedule.

Pharmacological

Excessive daytime sleepiness and sleep attacks

Due to the considerable evidence of its efficacy [26, 27, 28, 29, 30], modafinil is thought to be a conservative therapy and is regarded as the first line treatment for

excessive daytime sleepiness and sleep attacks. A split dose strategy, either with 200 mg at 07:00 and 12:00 or 400 mg at 07:00 and 200 mg 12:00, is advisable [31].

A more recent therapeutic attitude, based on the results from two studies, consists of using sodium oxybate at a starting dose of 4.5 g/night divided into two equal doses of 2.25 g/night [32, 33]. Supplementation with modafinil is indicated in case of insufficient efficacy of sodium oxybate alone [34].

Cataplexy

For cataplexy the conservative clinical approach is to use the latest antidepressants, especially venlafaxine or atomoxetine, based on their recognized efficacy and the absence of major adverse effects. However, these drugs suffer from a lack of randomized, double-blind, placebo-controlled clinical trials in narcoleptic patients. A more recent therapeutic approach is based on several randomized, double-blind, placebo-controlled clinical trials (US Xyrem® Multicenter Study Group 2002, 2004; Xyrem® International Study Group 2005) [32, 33, 35]. It consists of using sodium oxybate according to the same rule as previously indicated and titrating the dose up to an adequate level, to obtain positive results and avoid adverse effects. Should these treatments be inefficient, tricyclic antidepressants (TCAs) or selective serotonin reuptake inhibitors (SSRIs) can be tried.

Disturbed nocturnal sleep

The conservative attitude is to use benzodiazepines or non-benzodiazepines. However, the best current treatment is sodium oxybate in two night doses.

Behavioral management of excessive daytime sleepiness

The recommendation that narcoleptic patients take naps is one of the few behavioral approaches for which there is strong objective evidence of therapeutic efficacy [36, 37, 38, 39]. In one study two napping strategies were tested: a single long nap placed 180° out of phase with the nocturnal midsleep time versus a series of five naps positioned equidistantly throughout the day [37]. The two protocols tested resulted in a reaction time improvement, but no difference between long and multiple naps was disclosed. This evidence strongly suggests that daily naps should be regarded as an essential therapy in the clinician's toolkit for treating excessive daytime sleepiness. They are best scheduled on a patient-by-patient basis.

Treatment of co-morbidities

Obstructive sleep apnea syndrome aggravates excessive daytime sleepiness. It should be treated no differently from the general population. Until recently there was no documented effect of periodic leg movements during sleep on excessive daytime sleepiness in narcoleptic patients and no indication to treat them. However, results by Dauvilliers *et al*. suggest that the issue should be reconsidered [25]. Tricyclics and the SSRIs may trigger or exacerbate RBD. Despite the lack of a specific therapeutic trial in narcoleptic patients, clonazepam is recommended. According to Boeve *et al*., melatonin at a dose of 3–13 mg/night would be successful in 57% of cases [40].

Conclusion

The issue of narcolepsy in the elderly has not received all the attention it deserves. Narcolepsy does not develop after 55–60 years of age, a phenomenon for which there is no clear explanation. Excessive daytime sleepiness is a lifelong symptom while the other symptoms may abate or even vanish with age, in favor of a different pathophysiology. REM sleep behavior disorder and olfactory dysfunction are frequently seen features of narcolepsy. Yet they do not predict the future occurrence of parkinsonism, as they do in normal subjects. Parkinsonism and primary degenerative dementia do not develop in narcoleptic patients, suggesting that narcoleptic symptoms might be protective against these conditions. Finally, the treatment of narcolepsy in older adults is essentially the same as for younger patients, with the exception that behavioral strategies are easier to implement in older subjects due to their more flexible schedules.

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Part 3
Chapter
21

Sleep disorders in the elderly

Movement disorders in the elderly

Kai Spiegelhalder and Magdolna Hornyak

Introduction

Restless legs syndrome (RLS) is considered to be the most common sleep-related movement disorder in the elderly, although, in a broader sense, parasomnias like somnambulism and REM sleep behavior disorder as well as Parkinson's disease and epilepsy also belong to this category. Restless legs syndrome typically presents with an urge to move the legs, caused or accompanied by unpleasant sensations in the affected limbs, which lead to the more precise labeling of RLS as a sensorimotor disorder. Symptoms appear or worsen with rest and are at least temporarily relieved by motor activity. A prominent feature of the disorder is the circadian rhythmicity of the symptoms, with onset or increase in the evening or at night. According to this, sleep disturbance with prolonged sleep latency and increased wake after sleep onset is the most frequent reason for RLS patients to seek medical aid.

Epidemiological studies concerning the age distribution of RLS showed a 5–10% prevalence with a strong increase in the elderly [1, 2]. Restless legs syndrome symptoms are usually mild at onset in early adulthood and progress with advancing age. Studies suggest two phenotypes of the disorder, namely early-onset RLS with a significantly higher incidence of affected relatives and late-onset RLS. Treatment is generally not sought until the fourth decade [3]. Most epidemiological studies found the prevalence in women to be approximately twice as high as in men [1, 2]. The increased prevalence in women seems to be associated with the number of births [2].

The disorder has a high impact on sleep quality [4] and quality of life [2] but remains often unrecognized or misdiagnosed. In a study conducted from 2002 to 2003 general physicians made the correct diagnosis in less than 10% of cases [5]. Restless legs syndrome is still being referred to as "the most common disorder you never heard of." According to several studies, in those 60 years or older the prevalence of RLS is between 9% and 20%. The prevalence of persons needing medical treatment is estimated to be one-fifth up to one-third of the affected individuals, that is 2–6% of the elderly [5]. In the elderly, RLS might be even more under-diagnosed as some of these patients are not able to express complaints in as detailed and clear a manner as the general adult population. For this reason, the accurate diagnosis and therapy of the disorder may substantially improve the quality of sleep and life in this patient population.

In this chapter, we attempt to give a summary of the recent knowledge on diagnosis, etiology, and treatment of RLS in the elderly.

Diagnosis of restless legs syndrome

Current diagnostic criteria of RLS were established in 2003 [4, 6] and are presented in Table 21.1. In general, RLS is a clinical diagnosis and is based on the patient's description. In the elderly, the ability to express experienced bodily sensations verbally may be limited by the impact of co-morbid conditions such as cognitive impairment, speech disorders, or aphasic syndromes. Furthermore, cognitive deficits might be induced or exacerbated by RLS itself [7]. Due to this, a modification of diagnostic criteria in this special group of patients has been proposed [6] emphasizing the inclusion of behavioral indicators and supportive features within the diagnostic work-up. These modified diagnostic criteria for the elderly are presented in Table 21.2.

The disorder typically presents with an urge to move the legs, which is accompanied or caused by unpleasant sensations. Even young patients often have difficulties in describing these sensations except as to say that they are uncomfortable and deep inside the legs. Some patients report sensations like "tension," "crawling," "tearing," "burning," "electric current," or "painful." According to the modified diagnostic criteria for elderly patients, rubbing or kneading the legs and groaning while holding the lower extremities may indicate the patient's unpleasant sensations and the urge to move [6].

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Table 21.1. Diagnostic criteria for RLS [4, 6]

Essential criteria:
1. An urge to move the legs, usually accompanied or caused by uncomfortable and unpleasant sensations in the legs. (Sometimes the urge to move is present without the uncomfortable sensations and sometimes the arms or other body parts are involved in addition to the legs.)
2. The urge to move or unpleasant sensations begin or worsen during periods of rest or inactivity such as lying or sitting
3. The urge to move or unpleasant sensations are partially or totally relieved by movement, such as walking or stretching, at least as long as the activity continues
4. The urge to move or unpleasant sensations are worse in the evening or night than during the day or only occur in the evening or night. (When symptoms are very severe, the worsening at night may not be noticeable but must have been previously present.)
Supportive clinical features of RLS:
1. Positive family history of RLS
2. Response to dopaminergic therapy
Nearly all people with RLS show at least an initial positive therapeutic response to either levodopa or a dopamine-receptor agonist. This initial response is not, however, universally maintained
3. Periodic limb movements (during wakefulness or sleep)
Associated features of RLS:
1. Natural clinical course
The clinical course of the disorder varies considerably
2. Sleep disturbance
Disturbed sleep is a common major morbidity for RLS and deserves special consideration in planning treatment
3. Medical evaluation/physical examination
The physical examination is generally normal and does not contribute to the diagnosis except for those conditions that may be co-morbid or secondary causes of RLS

All four essential criteria are necessary for the diagnosis; the supportive criteria can help resolve any diagnostic uncertainty.

Restless legs syndrome symptoms improve by moving the affected limbs and worsen with rest. In the elderly, excessive motor activity in the lower extremities and subsequent reduction of the above-mentioned signs of leg discomfort are regarded as a diagnostic criteria for RLS. Additionally, for diagnosing RLS in the elderly, signs of leg discomfort must be exclusively present or worsen during periods of rest or inactivity.

RLS typically presents with a circadian rhythmicity of the symptoms with onset or increase in the evening or at night. This condition must also be given for diagnosing RLS in the elderly. With disease progression, earlier onset of symptoms during the day and in other parts of the body, most often in the arms, may occur.

Generally, it is important to obtain a detailed history of family members and of care-givers in diagnosing RLS in the impaired elderly. Conditions mimicking RLS like painful neuropathy, arthritic conditions, neuroleptic-induced akathisia, pruritus, leg cramps, and vascular insufficiency especially require carefully differentiated consideration in this patient group.

Periodic leg movements during sleep (PLMS) serve as supportive criteria for diagnosing RLS in both young and elderly patients. Periodic leg movements during sleep are a sleep phenomenon with periodic episodes of repetitive stereotyped leg movements [8, 9] and are characterized by the extension of the big toe in combination with flexion of the ankle, knee, and sometimes the hip. The muscle that is most frequently involved in the generation of PLMS is the tibial anterior muscle [9]. In polysomnographic studies, 80–90% of RLS patients reveal an elevated number of PLMS [10]. Generally, a PLMS index (number of PLMS per hour of sleep) greater than 10 is considered to be pathological. However, PLMS may also frequently occur in other sleep disorders such as narcolepsy, sleep apnea syndrome, or REM sleep behavior disorder and in elderly subjects without any sleep disturbance [11]. However, the time structure of PLMS might differ in different disorders following more detailed analyses [12]. Most RLS patients also show periodic leg movements while awake (PLMW).

Table 21.2. Diagnostic criteria for the diagnosis of probable restless legs syndrome in the cognitively impaired elderly (all five essential criteria are necessary for the diagnosis) [4, 6]

Essential criteria:
1. Signs of leg discomfort such as rubbing or kneading the legs and groaning while holding the lower extremities are present
2. Excessive motor activity in the lower extremities such as pacing, fidgeting, repetitive kicking, tossing and turning in bed, slapping the legs on the mattress, cycling movements of the lower limbs, repetitive foot tapping, rubbing the feet together, and the inability to remain seated are present
3. Signs of leg discomfort are exclusively present or worsen during periods of rest or inactivity
4. Signs of leg discomfort are diminished with activity
5. Criteria 1 and 2 occur only in the evening or at night or are worse at those times than during the day
Supportive criteria:
1. Dopaminergic responsiveness
2. Patient´s past history – as reported by a family member, care-giver or friend – is suggestive of RLS
3. A first degree, biological relative (sibling, child, or parent) has RLS
4. Observed periodic limb movements while awake or during sleep
5. Periodic limb movements of sleep recorded by polysomnography or actigraphy
6. Significant sleep-onset problems
7. Better-quality sleep in the day than at night
8. The use of restraints at night (for institutionalized patients)
9. Low serum ferritin level
10. End-stage renal disease
11. Diabetes
12. Clinical, electromyographic, or nerve-conduction evidence of peripheral neuropathy or radiculopathy

A severity scale for RLS symptoms, the International Restless Legs Syndrome Study Group Rating Scale (IRLS), has been developed and validated [13]. It comprises ten RLS-related questions that assess symptom frequency and intensity as well as the impact of the disorder on daytime functioning. The overall score ranges from 0 to 40: 0 to 10 points indicate mild symptoms, 11 to 20 points indicate moderate symptoms, 21 to 30 points indicate severe symptoms, and 31 to 40 points indicate very severe symptoms. The IRLS has been widely used in treatment studies to monitor outcome and is also suitable for clinical applications.

Especially in the elderly, RLS is often secondary to other diseases (for summary see Table 21.3). The clinically most relevant secondary causes of RLS are iron deficiency and end-stage renal disease [14]. RLS may also occur or worsen due to the effect of drugs, especially neuroleptics and antidepressants.

Etiology of RLS

The pathogenesis of RLS is still unknown [15] and no animal model is available that mimics all the manifestations of the disorder [16]. Pharmacological studies of dopaminergic drugs ([17], see also the treatment section) provided overwhelming evidence for a primary role of the dopaminergic system in the development and maintenance of RLS. According to this, dopaminergic drugs are the treatment of choice. However, cerebral neuroimaging studies concerning the

Table 21.3. Secondary forms of RLS

Medical condition	Prevalence (%)
Pregnancy	26
M. Parkinson	8–21
Sarcoidosis	52
Charcot-Marie-Tooth disease, type 2	37
Rheumatoid arthritis	15–25
Polyneuropathy	1–36
Multiple sclerosis	36
HIV	30

dopaminergic system produced inconsistent results. While presynaptic dopamine transporter binding seems to be normal in RLS patients, post-synaptic D2-rector binding might be decreased [18]. Dysfunction of dopaminergic transmission might also play a key role in the spinal cord, especially in the development of augmentation ([19], see also treatment section).

A potential central role of iron pathology for the pathophysiology of RLS is indicated primarily by secondary forms of the disorder, i.e. iron deficiency, end-stage renal disease, and pregnancy [20]. There might be a connection between iron and dopamine pathology as iron is a co-factor for tyrosine hydroxylase, which is the rate-limiting enzyme for dopamine synthesis. MRI studies using a special measurement suggest an iron deficiency that is especially evident in the substantia nigra [21].

Functional magnetic resonance imaging studies suggest that sensory leg discomfort is associated with increased neuronal activity in the contralateral thalamus [22] and bilateral in the cerebellum [22, 23]. As PLMW seem to be associated with additional bilateral neuronal activity in the red nuclei and in the brainstem [22], a circuitry involving the red nucleus, the inferior olive, and the cerebellum has been suggested to play an important role in the pathophysiology of RLS [15]. Future studies might use combined EMG-fMRI-recordings for identifying cerebral correlates of PLMW [23].

Results of three morphometric studies investigating structural cerebral changes in RLS patients are inconsistent. Two studies found gray matter alterations in the pulvinar and in the primary somatosensory cortex when comparing medicated RLS patients with healthy controls [24, 25] indicating alterations of the primary somatosensory system in the disorder. However, one study did not find these alterations in unmedicated RLS patients [26].

Two recent genetic studies found an association between a genetic variance in the BTBD9 gene and an increase in the prevalence of RLS [27, 28]. In the study of Winkelmann *et al.* [27] two more genetic variances were found with one of them (MEIS1) being known for being involved in playing a role in limb development. According to this, RLS might have components of a developmental disorder. Generally, there seems to be a significant involvement of genetic factors in the etiology of RLS.

Treatment of restless legs syndrome in the elderly

In Table 21.4, the most commonly prescribed drugs for RLS are presented with dosing and side effects. Dopaminergic drugs are the first-line treatment choice in RLS; however, treatment is symptomatic as the etiology of RLS is not known. According to the timely occurrence of symptoms, RLS medications are usually taken at bedtime. Up to now, no studies have been published investigating treatment effects specifically in the elderly.

The dopamine precursor levodopa in combination with a dopa-decarboxylase inhibitor is an effective therapeutic agent with high tolerability and without serious side effects, also in patients with concomitant medical disorders. For this reason, it might be considered as first-line treatment in the elderly. It improves

Table 21.4. Dopaminergic medications for the treatment of RLS

Medication	Daily dose rate	Side effects
Levodopa/dopa-decarboxylase inhibitor	100/25–400/100 mg	Diarrhea, nausea, dyspepsia, reduced general drive, muscle weakness, somnolence, headache
Pramipexole	0.125–0.75 mg	Nausea, dizziness, fatigue, somnolence, headache, orthostatic hypotension
Ropinirole	0.25–4 mg	Nausea, dizziness, fatigue, somnolence, headache, orthostatic hypotension
Rotigotine (transdermal patches)	1–3 mg	Nausea, dizziness, fatigue, skin reactions at the patch site, orthostatic hypotension
Cabergoline	0.5–2.0 mg	Nausea, dizziness, fatigue, somnolence, headache, orthostatic hypotension, cardiac valvular disease
Pergolide	0.25–0.75 mg	Nausea, dizziness, fatigue, somnolence, headache, orthostatic hypotension, cardiac valvular disease

RLS symptoms, quality of sleep, and quality of life [29, 30].

The benefit of dopaminergic agonists in RLS has also been proven in several studies. Their use, however, has to be carefully indicated in the elderly because of possible interactions with multiple other medications and of side effects such as orthostatic hypotension, nausea, or seldomly dizziness.

Pramipexole and ropinirole are the most extensively studied drugs for RLS. Concerning pramipexole, several large randomized controlled trials have been published [31, 32] and indicate significant benefits, namely reducing RLS symptoms and increasing quality of sleep and quality of life. Mean improvement in the IRLS score in the two largest studies was 3 to 7 points better in the treated groups when compared with placebo. Surprisingly, there were no differences in IRLS score reduction between pramipexole dosing groups [31]. Three 12-week studies of ropinirole versus placebo were conducted in large samples of RLS patients [33, 34, 35]. In these studies, mean IRLS score was reduced 2.5 to 4 points more in the ropinirole group than in the placebo group. Pramipexole and ropinirole have been compared in a meta-analysis of the literature as comparative trials are lacking. According to this analysis, pramipexole is superior to ropinirole regarding efficacy and tolerability [36].

The ergot derivates (cabergoline, pergolide) can only be considered today when non-ergot derivates and other treatment options are not sufficient because of the increased risk of valvular heart disease [37], although both cabergoline [30, 38, 39] and pergolide [40] are proven to be effective in improving RLS symptoms significantly. The only large-scale comparative study between dopaminergic agents in patients with RLS found that cabergoline was more effective in reducing RLS symptoms than levodopa in combination with benserazide [30]. However, adverse events were more prevalent in the cabergoline group, indicating a higher tolerability for levodopa/benserazide. Most frequent adverse events in both groups were gastrointestinal symptoms.

Transdermal application can be an alternative route for treating RLS with dopamine agonists. This route of administration ensures a constant rate of drug delivery, more steady serum concentration, and reduction in daytime breakthrough symptoms. According to this, this treatment strategy may be especially useful in patients experiencing severe RLS with symptoms over most of the day. Transdermal formulations include the dopamine agonists rotigotine and lisuride. Rotigotine reduced IRLS scores 5 to 7 points more than placebo in a recent 6-week multicenter dose-finding study [41].

Up to now there have been no published comparative studies of dopamine agonists. Furthermore, it should be pointed out that no long-term studies exceeding 1-year treatment period exist. The main complication of dopaminergic treatment of RLS with levodopa and dopamine is the development of augmentation [42]. The main characteristic of augmentation is the medication use-related increase of symptom severity, which typically occurs after an initial improvement. It can manifest as an increased intensity of the urge to move, an increased intensity of the unpleasant sensations, an earlier onset of symptoms, or an expansion of the symptoms to previously unaffected limbs or body parts. Standard diagnostic criteria for the clinical diagnosis of RLS augmentation have been developed recently [43]. In patients with augmentation, elevating the dosage of the dopaminergic substance associated with the augmentation usually leads to a transient relief of symptoms, lasting sometimes only for a few weeks. The occurrence of clinically meaningful augmentation usually demands a change of the treatment regime. However, up to now, there are no clinical studies concerning the treatment of augmentation.

Opioids seem to have a long-term efficacy in the treatment of RLS and are well tolerated in the elderly; however, the number of clinical studies on that topic is limited [44]. Oxycodone is the best-studied opioid for the treatment of RLS patients. Clinical or polysomnography monitoring for the development of sleep apnea is recommended in patients on long-term opioid therapy. Anticonvulsants like gabapentine can be efficient in patients with painful paresthesias [45]. Benzodiazepines and benzodiazepine-like hypnotics such as zopiclone or zolpidem may improve sleep also in RLS patients, mainly in those with less severe symptoms. However, hypnotics need special attention when prescribed in the elderly as benzodiazepines increase the risk for falls and cognitive impairment in this group. There is some evidence that iron supplementation with intravenous iron dextran is effective in low-ferritin patients and in patients with RLS secondary to uremia [46]. Magnesium was found to be effective in decreasing PLMS in a pilot study investigating RLS patients and insomniacs with elevated PLMS [47]. Additionally, psychological therapeutic strategies for

improving RLS coping skills and quality of life are highly accepted and might help RLS patients to adjust to their disorder [48].

Conclusion

Restless legs syndrome is a clinical diagnosis with a prevalence of 9–20% in the elderly. An estimated one-fifth to one-third of the affected persons needs medical treatment. A detailed history of the patient, and if necessary of the care-givers, is important in the diagnosis. Restless legs syndrome should be considered in the differential diagnosis of any older patient with sleep disturbances and/or paresthesias of the limbs. The high association of RLS with several disorders has to be borne in mind. Some pharmacological agents could also trigger or exacerbate RLS. Dopaminergic drugs are the first-line treatment option in RLS. The most clinically relevant problem with dopaminergic drugs in treating RLS is the development of augmentation, a medication use-related increase of symptoms, which usually occurs after an initial improvement. In severe cases, augmentation demands a switch of medication.

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Part 3
Chapter
22

Sleep disorders in the elderly

REM sleep behavior disorder in the elderly

Luigi Ferini-Strambi

Introduction

REM sleep behavior disorder (RBD) is a parasomnia characterized by complex motor activity during REM sleep, usually associated with dream mentation [1]. Patients have elaborate nocturnal motor behaviors, such as screaming, punching, grasping, that are potentially harmful for themselves or their bed partner [1, 2]. In RBD patients polysomnographic (PSG) recording reveals intermittent or complete loss of REM sleep muscle atonia and excessive phasic electromyographic (EMG) activity during REM sleep [1].

RBD affects mainly men after the age of 50 years although the prevalence remains largely unknown. A study performed among 1034 individuals aged 70 years and more in the Hong Kong area found self-injury during sleep in 8 patients, 4 of whom received a PSG diagnosis of RBD yielding an estimated prevalence of 0.04% [3].

RBD may be idiopathic or associated with neurodegenerative diseases, most often the alpha-synucleinopathies, such as Parkinson's disease (PD) [4, 5, 6], dementia with Lewy bodies (DLB) [7, 8], and multiple system atrophy (MSA) [9, 10]. Moreover, a number of neurological conditions with the involvement of the brainstem may result in RBD. If no neurological signs or central nervous system (CNS) lesions are found, RBD is defined as "idiopathic." This form accounts for up to 60% of the observed cases in the largest published series of RBD patients [2, 11, 12].

Table 22.1 shows the clinical features of RBD.

Pathogenesis of RBD

The pathogenesis of RBD is still not clear. Multiple neural substrates, mainly located in the brainstem, contribute to REM sleep atonia and may be involved in the pathogenesis of RBD. These include the ventral mesopontine junction, the laterodorsal and pedunculopontine tegmental nuclei (LTD-PPN), the locus coeruleus (LC) and the peri-LC area in the pons and the magnocellularis (NMC), gigantocellularis (NGC), and paramedianus (NPM) nuclei in the medial medulla [13]. An experimental animal model of RBD has been obtained in cats after dorsal pontine lesion, and a variety of behavioral manifestations have been found to be dependent on specific sites of pontine lesions [14, 15]. Studies in the cat suggested that there are two motor systems involved in normal REM sleep: one for generating muscle atonia and one for suppressing locomotor activity [16]. Lesions in the LC and the peri-LC area cause REM sleep without atonia (RSWA).

Recently, some authors reported a case of a 68-year-old man with RBD after a right pontine tegmental ischemic lesion [17]. This case provides evidence that the unilateral pontine lesion by itself is sufficient to cause RBD. In humans, meso-striatal dopaminergic neurons might also be implicated and brain imaging studies, performed in idiopathic RBD patients using PET or SPECT, showed a decreased striatal dopaminergic innervation [18] and a reduced pre-synaptic striatal dopamine (DA) transporter binding, respectively, in RBD [19], similar to what is observed in patients with early PD.

The notion of an impairment of the striatal dopaminergic system is also supported by data from a prospective study performed on idiopathic RBD showing that 11 out of 29 (38%) male patients developed a parkinsonian syndrome within 3.7 years from the RBD onset [5]. The study has been recently updated, showing that 17 out of 26 (65.4%) idiopathic RBD patients originally enrolled eventually developed a parkinsonian disorder (N = 16) and/or a dementia without parkinsonism (N = 1) after an average interval of 13.3 years from RBD onset, although in nine patients RBD was still idiopathic after a mean of 20.3 years [20]. Another study found the eventual emergence of a parkinsonian syndrome in 21% of 19 idiopathic RBD patients, after a mean interval of 11 years from the RBD onset and a mean follow-up of 4.6 years [21],

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Table 22.1. Clinical features of REM sleep behavior disorder

Age of onset: after 50 years
Male gender predilection
Course is progressive (spontaneous remissions are very rare)
Vocalization, swearing, screaming
Motor activity varies from simple jerks to complex motor phenomena (especially in the latter half of the sleep period)
Patients report dreams in which they are attacked by animals or unfamiliar people and they would either fight back in self defense or attempt to flee
Complications include sleep-related injuries to self or bed partner, and disruption of the bed partner's sleep
One-third of patients with newly diagnosed Parkinson's disease have RBD, and 90% of patients with multiple system atrophy have RBD (RBD often precedes the neurodegenerative disorders by years)

while others reported the occurrence of neurological signs in 36% of 20 idiopathic RBD patients longitudinally followed for a period ranging from 6 months to 10 years [22]. Iranzo *et al.* [23] retrospectively evaluated 44 consecutive patients (mean age = 74 years) with at least 2 years of clinical follow-up after a diagnosis of idiopathic RBD and found that 20 (45%) of the patients developed PD (9 cases), DLB (6 cases), MSA (1 case), and mild cognitive impairment (4 cases). It is known that PD may be classified into different clinical subtypes that seem to have different patterns of disease progression: motor functions deteriorate more rapidly in the cases with predominant akinesia and rigidity, while tremor-predominant cases have a more benign evolution. Interestingly, it has been reported that PD patients with RBD had mostly the non-tremor-predominant subtype, and RBD preceded PD only when parkinsonism started after the age of 50 years [6]. The age of onset of the neurodegeneration seems to be less crucial for the other forms of neurodegenerative diseases associated with RBD such as MSA and DLB. Probably in these two diseases the pathology is more severe and involves earlier more critical areas for RBD generation in the brainstem. One study found that 44% of 35 patients affected by RBD and MSA developed RBD from 1 to 19 years before the appearance of MSA [9]. In 77% of 31 patients with RBD associated with DLB, the latter had heralded the onset of the dementia by an average period of 9 years [8].

Based on these data, idiopathic RBD may represent, in a certain number of cases, an early manifestation of an impending neurodegenerative disease. Recent studies have examined various neurophysiological and neuropsychological functions in idiopathic RBD, in order to detect early signs of CNS dysfunction associated with the REM sleep motor dyscontrol, and several abnormalities have been observed in such patients, challenging the concept of "idiopathic" RBD. The recent converging evidences on CNS dysfunction during both wakefulness and sleep in idiopathic RBD are reviewed.

Neurovegetative and olfactory functions in idiopathic RBD

Braak and colleagues have recently identified a stereotyped pattern of evolution in Lewy body disease (PD and DLB) [24]. Lewy body pathology begins in the anterior olfactory nucleus and in the lower brainstem nuclei, affecting olfactory and autonomic functions initially, and progressing rostrally to ultimately affect the cerebral cortex. It is known that synucleinopathies are frequently associated with autonomic impairment, often preceding motor symptoms. In PD, manifestations of autonomic dysregulation are frequent, including orthostatic hypotension, reduced heart rate variability, and impairment in the sudomotor, gastrointestinal and urinary functions [25, 26]. In DLB, recurrent syncopes represent a supportive feature for the diagnosis and they may precede the manifestations of cognitive decline [27]. In MSA, autonomic failure may be the dominant finding in the clinical picture [26].

A lack of autonomic activation during the nocturnal dream-enacting motor behaviors has been occasionally observed in RBD patients. However, several years ago it was reported that idiopathic RBD patients not only have a reduced tonic and phasic heart rate variability during sleep, but the majority of these patients also have an impairment in one or more tests assessing sympathetic or parasympathetic functions during wakefulness, compared to age- and sex-matched

healthy controls [28]. In agreement with these results, Fantini *et al.* found a reduced cardiac activation related to periodic limb movements (PLMS) during stage 2 sleep in patients with idiopathic RBD compared to age- and sex-matched patients affected by restless legs syndrome (RLS) [29]. A recent study assessed autonomic cardiac regulation and respiratory responses during sleep in subjects with idiopathic RBD (mean age = 63.4 years), compared with controls (mean age = 63.9 years), using spectral analysis of R-R variability and respiration variability [30]. The authors found that REM-related cardiac and respiratory responses were absent in RBD patients. The LC/peri-LC complex is implicated in REM sleep generation, and it is also known to provide extensive noradrenergic innervation to all CNS areas involved in the integration of sensory and motor responses to arousals and stressful situations. Neuronal damage in this area could be a factor implicated in both blunted and absent autonomic response in association with motor activity [28, 29] and during REM sleep [30].

Olfactory dysfunction that involves odor identification, detection, and differentiation is a frequent feature of PD and DLB, often preceding by several years the motor and/or cognitive symptoms [31]. Recently, the olfactory functions have been investigated in idiopathic RBD [32]. Fifty-four PSG-confirmed idiopathic RBD patients (44 male, 10 female; mean age: 69.2 ± 8.3 years) and 54 age-matched controls underwent a Brief Smell Identification Test (B-SIT), which is a smaller and cross-cultural neutral 12-items version of the University of Pennsylvania Smell Identification Test (UPSIT). This test has been developed to assess the individual ability to perceive and name an odorant. Participants were free of psychotropic medication that could influence dopamine transporter binding and/or olfactory function, and none had a history of nasal surgery, significant head trauma, hepatitis, endocrine disorders, or allergies. A marked olfactory impairment was observed in the RBD group compared to control subjects (mean B-SIT score: 7.1 ± 2.5 vs. 9.4 ± 1.8, $p < 0.0001$). The deficit in recognizing paint thinner odorant showed the highest positive predictive value (0.95) for identifying idiopathic RBD, and is exactly the same olfactory deficit found in PD patients.

EEG activity in idiopathic RBD

Fantini *et al.* [33] recently found higher theta power in the frontal, temporal, and occipital regions with a lower beta power in the occipital region during wakefulness in idiopathic RBD patients (mean age = 66.2 years), compared to age- and sex-matched healthy controls. Also, a lower dominant occipital frequency (DOF) during wakefulness was found in idiopathic RBD patients. Indeed, the whole mean EEG power spectrum recorded in the occipital region appeared to be shifted towards slower frequencies, compared to controls, although significant differences were noted for the increase in theta and the decrease in beta2 bands only. Four out of the fifteen idiopathic RBD patients presented a DOF value in the theta range (below 8 Hz), a value considered to be pathological. During REM sleep, beta power in the occipital region was lower in RBD patients compared to controls, whereas no difference in any region was observed in the amount of theta power. Since only theta and beta2 bands showed significant differences, the ratio of the power in theta over beta2 (TH/BE2) was calculated as an index of cortical slowing that could differentiate RBD patients from controls.

Therefore, the authors postulated that the slowing of the EEG found in idiopathic RBD patients might be associated with subtle cognitive deficits and those patients showing the highest values of TH/BE2 ratio may represent a subgroup of subjects who are more likely to develop eventually a degenerative disorder associated with dementia. Alternatively, the distribution of the TH/BE2 ratio values might reflect the severity of the neurodegenerative process associated with RBD. Objective measures, such as percentages of muscle atonia or of phasic EMG activity during REM sleep, also failed to correlate with the EEG slowing. These results support the notion of the heterogeneity of RBD, with some patients, but not all, presenting a slowing of the EEG and being possibly at higher risk for developing cognitive impairment and eventually dementia.

This hypothesis is supported by electrophysiological studies conducted in patients with cognitive impairment. For example, a slowing of the EEG is commonly observed in the early stages of dementia, such as in Alzheimer's disease and in patients with mild cognitive impairment. Indeed, an increase of theta activity is believed to represent a sensitive index of early cognitive deterioration [34]. A slowing of the DOF is also frequently observed in neurodegenerative conditions such as AD, PD, and DLB [35, 36].

Moreover, similarities may be observed between the topographical distribution of the EEG slowing in

idiopathic RBD patients (predominant involvement of the occipital region) and the pattern of the perfusional and metabolic impairment observed in DLB and in PD [37, 38]. These observations are in agreement with the notion of a common pathophysiological mechanism between these conditions.

Neuropsychological assessment in idiopathic RBD

Cognitive functions are apparently preserved in idiopathic RBD, as assessed by the standard clinical evaluation. Neither patients nor their relatives usually report symptoms of cognitive decline, and the Mini Mental State Examination (MMSE) score has been reported as normal. However, a recent study evaluated patients with idiopathic RBD (mean age = 70.0 years; average duration of symptoms 5.7 ± 5.3 years) by an extensive neuropsychological assessment for a broad range of cognitive functions [39]. The results of this study showed, for the first time, that idiopathic RBD patients have impairment in both visuo-spatial constructional performances and visuo-spatial learning compared to age- and sex-matched controls, as assessed by the Rey-Osterreith's Complex Figure Test and the Corsi Supraspan Learning Test, respectively. Other authors [40] reported that, compared to 23 age-matched controls, 23 patients with idiopathic RBD (mean age = 67.0 years) showed poorer performances on tests of working memory/attention, visual memory, executive functions, and long-term verbal memory.

The similarity between the type of cognitive deficits found in idiopathic RBD and those observed in patients with DLB and PD, with or without dementia, is remarkable and supports the hypothesis that a common pathophysiological mechanism underlies these two conditions. Since RBD often heralds a Lewy body disease (LBD), either PD or DLB, by several years, it may be hypothesized that the neuropsychological deficits observed in idiopathic RBD represent an early manifestation of one of these neurodegenerative diseases.

Interestingly, a recent paper [41] evaluated 34 patients with PD (18 patients with a concomitant RBD, mean age = 65.6 years, and 16 patients without RBD, mean age = 65.1 years) and 25 healthy controls (mean age = 66.8 years) with a comprehensive neuropsychological assessment. Patients with PD+RBD showed poorer performance on the tests measuring executive functions and visuo-spatial and visuo-perceptual processing compared to both PD patients without RBD and controls.

Dreams in RBD

RBD patients typically report vivid, unpleasant, and action-filled dreams that are generally congruent with the observed behaviors, although no study has systematically assessed dream characteristics in RBD. Regardless of the etiology, it is commonly assumed that the lack of motor inhibition during REM sleep in these patients allows the enactment of the oneiric imagery. Patients with RBD usually report dreams in which they are attacked by animals or unfamiliar people and they would either fight back in self defense or attempt to flee [42]. It has also been observed that the violence and aggressiveness displayed during nocturnal behaviors is in contrast with the often placid and mild-mannered daytime temperament [42].

A recent study [43] systematically assessed dream characteristics and daytime aggressiveness in RBD and controls. Twenty-nine RBD patients (18 idiopathic, 11 symptomatic: 7 PD, 3 MSA, 1 LBD) and 63 age- and sex-matched controls were asked to recall their most recent dreams and to fill in the Aggression Questionnaire (AQ). Only 32 (82%) RBD patients (mean age = 68.5 ± 7.6 years) and 30 (47.6%) controls (mean age = 69.1 ± 5.9 years) were able to remember their dreams and a total of 83 and 60 dreams were collected in the two groups, respectively. Subjects were asked to recall one or more recent dreams. First, a trained interviewer collected verbatim descriptions of these dreams. Then a semi-structured interview was performed in order to assess more precisely specific elements of the dream such as characters, social interactions, activities, success and failures, misfortune and good fortune, emotions, settings, objects, and descriptive elements, as described in the Hall and Van De Castle method [44]. The Hall and Van De Castle method is the most comprehensive and widely used empirical system for dream content analysis. RBD patients showed a higher percentage of "dream with at least one aggression" than controls (63% vs. 16%, $p < 0.00001$), a higher aggression/friendliness interactions ratio (90% vs. 55%; $p < 0.01$), and a greater frequency of animal characters (18% vs. 4%; $p = 0.001$). In contrast to controls, none of the RBD patients had "dreams with at least one element of sexuality" (0% vs. 11%, $p < 0.0001$). No correlation was observed between any indicator of dreams' aggressiveness and either age, duration, or frequency of RBD symptoms.

The AQ is a validated test developed to assess aggression, which consists of 29 items; a validated Italian version is available. The subjects rate each item on a five-point scale to indicate the degree to which the item is characteristic of themselves. The two groups did not differ in total AQ scores, except for a lower score on "physical aggressiveness" in RBD compared to control subjects (16.8 ± 6.7 vs. 20.8 ± 8.8; p = 0.03).

A lower prevalence of male characters characterized dreams of symptomatic RBD compared to idiopathic RBD, despite a similar gender distribution of dreamers in the two groups. The increased percentage of male characters in dreams is usually associated with a more threatening and aggressive dream content. If this is true, the observed male under-representation may reflect a milder aggressive content in symptomatic RBD, and this would be concordant with the observation that intensity of RBD manifestation often decreases as the neurodegenerative disease progresses.

This is the first study to quantitatively assess the dream characteristics in RBD. An increased occurrence of both aggression themes and animals is reported also in children's dreams, and their frequency decreases with age. Thus, one may hypothesize that a neurodegenerative process, often underlying chronic RBD, would lead to a release of archaic dream patterns. Alternatively, the elevated aggressiveness of dream content and the excessive EMG activity during REM sleep in RBD might be related to the hyperactivity of a common neuronal generator. The increased ability to recall dreams in RBD may be related to the peculiar dream content or it may reflect differences in memory processes.

Treatment of RBD

No double-blind, placebo-controlled study has been performed for any drug treatment for RBD. Clonazepam is currently regarded as the treatment of choice for RBD, and it is ineffective in only 10% of patients [42]. The initial dose is 0.5 mg at bedtime, and eventually the dose can be increased to 1 or 2 mg. Tolerance is very rare and the beneficial effects of clonazepam that start in the first week of treatment usually persist for several years.

Some studies have suggested a beneficial effect of melatonin (3–9 mg at bedtime) in RBD. In patients with contraindications to clonazepam, such as subjects with cognitive impairment, obstructive sleep apneas, or increased risk of falls, a treatment with melatonin should be preferred. Interestingly, clonazepam has little effect on EMG tone during REM sleep despite near complete suppression of clinical RBD, whereas partial restoration of normal EMG atonia in REM sleep has been observed in RBD patients treated with melatonin [16].

Drugs with controversial effects on RBD symptoms are levodopa and pramipexole [45]. The agents that tend to increase the frequency and/or severity of RBD are reported in the Table 22.2. All of these agents should be avoided in patients with RBD.

Conclusions

RBD is a male-predominant disorder that usually emerges after the age of 50 years. Some studies indicate that idiopathic RBD may be associated with a number of neurological abnormalities. These observations support the notion of RBD as an early manifestation of a more pervasive neurodegenerative process and challenge the concept of idiopathic RBD.

However, it should be noted that the neurophysiological and neuropsychological abnormalities reported in RBD affect a variable proportion of idiopathic RBD patients, but not the totality. Long-term follow-up studies revealed that a proportion of idiopathic RBD patients never develop other neurological illnesses, even several decades after the diagnosis of RBD. Idiopathic RBD seems to be characterized by heterogeneous clinical phenotypes, but data are still insufficient to identify specific subgroups of patients with possible implication in prognosis and/or treatment.

Further studies assessing the reciprocal relationship between neurophysiological parameters (EEG, autonomic, olfactory) and/or neuropsychological functions in these patients would help to identify specific phenotypes. With the improved life expectancy and the subsequent growth of the elderly population, the prevalence of neurodegenerative diseases has significantly increased, with high social costs. Therefore, it

Table 22.2. Agents that may increase the frequency/severity of REM sleep behavior disorder

Tricyclic antidepressants (particularly clomipramine and amitriptyline)
Monoamine-oxidase inhibitors (selegiline, phenelzine)
Selective serotonin reuptake inhibitors (particularly fluoxetine, mirtazapine)
Noradrenergic antagonists (bisoprolol, tramadol)
Chocolate

is crucial to detect early markers of neurodegeneration and to identify those subjects presenting with a higher risk of developing a neurodegenerative illness, in order to develop early intervention strategies. This may be critical to stopping or slowing down the impending neurodegenerative process and functional deterioration.

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Part 3
Chapter
23

Sleep disorders in the elderly

Sleep apnea in the elderly

Andrea H. S. Loewen, Marc J. Poulin, and Patrick J. Hanly

Introduction

Our current understanding of sleep apnea has evolved predominantly from the investigation of middle-aged adults without specific attention to the elderly population. Nevertheless, sleep apnea appears to be common in the elderly and its presentation to practitioners of sleep and geriatric medicine will grow in the years to come as the population ages. There are many challenges in how to deal with sleep apnea in the elderly including the criteria for diagnosis and management and its clinical relevance. Ultimately, many of these questions will need to be addressed by research studies that are specifically directed at the elderly. In this chapter we will review the current medical literature on this topic and, based on this information, provide some guidance on how to manage sleep apnea in the elderly.

Definition of sleep apnea

Sleep disordered breathing includes obstructive sleep apnea (OSA), central sleep apnea including Cheyne-Stokes respiration (CSR), and sleep hypoventilation. Sleep hypoventilation comprises a heterogeneous group of disorders ranging from central hypoventilation to conditions associated with impaired respiratory mechanics that are further compromised by transition from wakefulness to sleep. This chapter will focus on obstructive and central sleep apnea.

Obstructive sleep apnea (Figure 23.1a) is defined as 5 or more obstructive respiratory events per hour of sleep accompanied by nocturnal or daytime symptoms, or by 15 or more obstructive respiratory events per hour of sleep without accompanying symptoms [1]. Central sleep apnea (Figure 23.1b) is defined as 5 or more central respiratory events per hour of sleep. Cheyne-Stokes respiration is characterized by central apnea alternating with prolonged hyperpneas with a characteristic crescendo/decrescendo appearance [1]. Respiratory events may be apneas (cessation of airflow for at least 10 seconds) or hypopneas (at least 30% reduction of airflow lasting 10 seconds, associated with a drop in oxyhemoglobin saturation of 4% [1], [1a]).

The apnea–hypopnea index (AHI) is the number of apneas and hypopneas per hour of sleep. The respiratory disturbance index (RDI) refers to the number of apneas, hypopneas, and respiratory effort-related arousals per hour of sleep. The severity of sleep apnea is generally classified by the AHI. An AHI of less than 5 is considered to be normal, 5–15 is mild sleep apnea, 16–30 is moderate sleep apnea, and >30 is severe sleep apnea [2].

Significance of involuntary sleepiness

Since daytime sleepiness is an important symptom in the diagnosis and management of sleep apnea, it is important to know the prevalence of this complaint in the elderly population and whether it is a reliable symptom of sleep apnea. Daytime sleepiness can be assessed subjectively by questionnaires such as the Epworth Sleepiness Scale (ESS) and objectively by investigation in the sleep laboratory such as the Multiple Sleep Latency Test (MSLT). Elderly patients with sleep apnea report more sleepiness than elderly subjects without sleep apnea [3, 4] and they report a similar degree of sleepiness as young apneic subjects [5]. Objective evaluation of daytime sleepiness by MSLT demonstrates that healthy elderly subjects have a similar degree of sleepiness as younger adults [6]. Consequently, a complaint of daytime sleepiness in the elderly should not be attributed to normal aging, and should prompt further evaluation for an underlying cause including sleep apnea.

Prevalence of sleep apnea

The prevalence of sleep apnea has been well established in the middle-aged population. In a community-based study of subjects aged 30–60 years who had overnight polysomnography in the sleep laboratory, 24% of men

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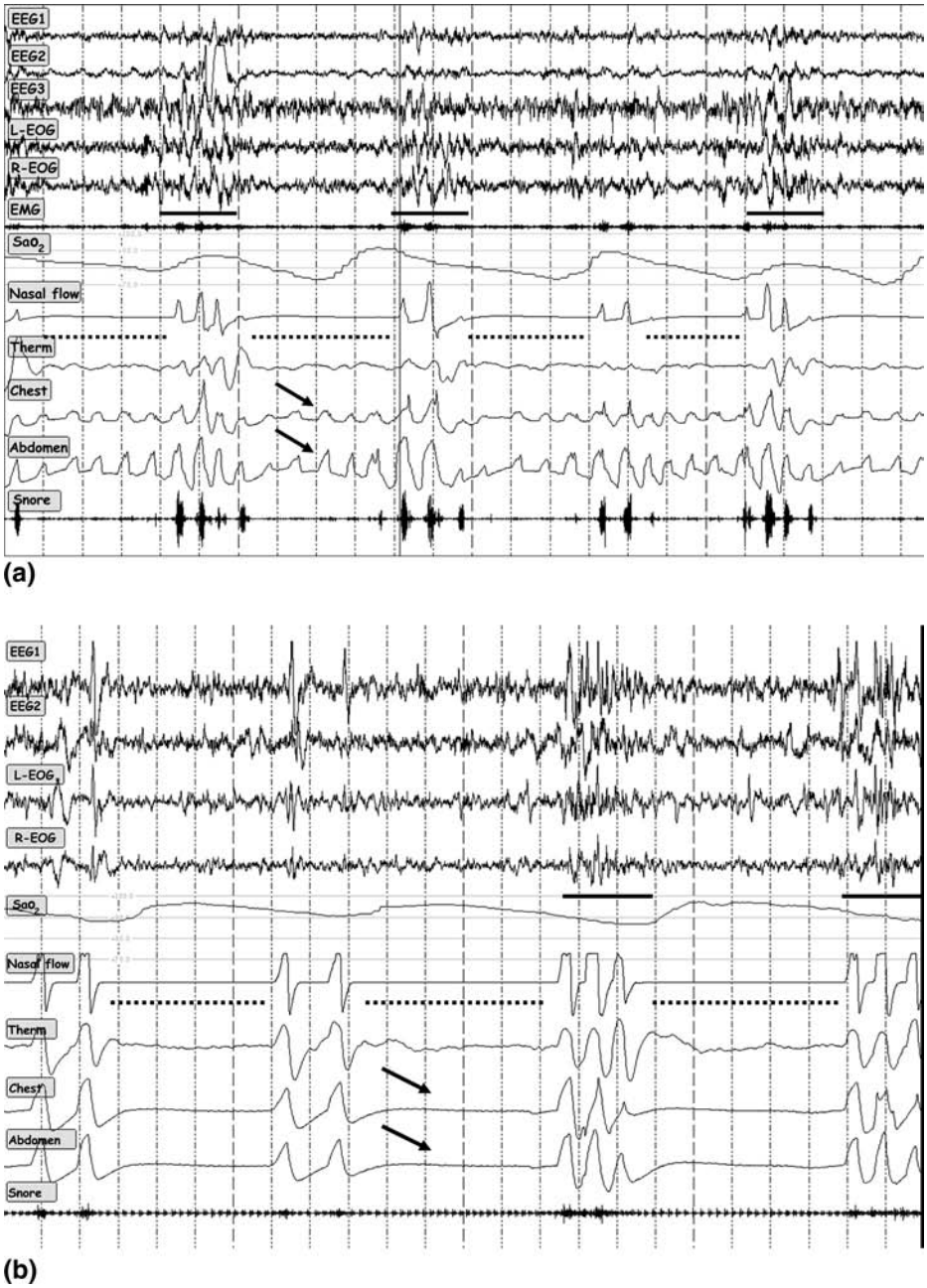

Figure 23.1. (a) Obstructive apnea during 2 minutes of non-rapid eye movement sleep. Recording includes 3-channel electroencephalogram (EEG), 2-channel electro-oculogram (L-EOG, R-EOG), sub-mental electromyogram (EMG), oxygen saturation (SaO_2), nasal airflow measured by nasal pressure, oral airflow measured by thermistor (Therm), chest and abdominal movement, and snoring. Note apnea (broken horizontal line) despite persistent respiratory efforts (arrows) associated with intermittent fall in SaO_2 and recurrent arousals from sleep (solid horizontal lines). (b) Central apnea during 2 minutes of non-rapid eye movement sleep. Recording includes 2-channel electroencephalogram (EEG), 2-channel electro-oculogram (L-EOG, R-EOG), sub-mental electromyogram (EMG), oxygen saturation (SaO_2), nasal airflow measured by nasal pressure, oral airflow measured by thermistor (Therm), chest and abdominal movement, and snoring. Note apnea (broken horizontal line) and absence of respiratory efforts (arrows) associated with intermittent fall in SaO_2 and recurrent arousals from sleep (solid horizontal lines).

and 9% of women had sleep apnea, defined as an AHI ≥5; furthermore, 2% of women and 4% of men had sleep apnea syndrome, defined as an AHI ≥5 accompanied by complaints of daytime sleepiness [7]. Studies of the elderly have used polysomnography both in the sleep laboratory and at home to investigate sleep apnea prevalence with results ranging from 18% to 62% [8, 9, 10, 11] (Table 23.1). Two of these studies categorized their results into different age groups, which indicated that the prevalence of sleep apnea increased with advancing age [9, 11]. In the Sleep Heart Health Study, the prevalence of sleep apnea plateaued after age 60 (Figure 23.2), but this may partially reflect lower enrolment of subjects over 60 years [11].

The apparent increased prevalence of sleep apnea in the elderly may be largely due to an increased prevalence of central sleep apnea associated with normal aging (Table 23.2). Bixler *et al.* evaluated 741 community-dwelling men aged 20–80 with polysomnography [12] and found that the prevalence of sleep apnea, reflected by an AHI ≥20, was 1.7% in those aged 20–44 years, 6.4% in those aged 65–100 years. However, central apneas accounted for most of the increase in apnea prevalence associated with advancing age. Furthermore, the severity of associated hypoxemia decreased with advancing age. In addition, sleep apnea syndrome (defined as an AHI ≥10 accompanied by daytime symptoms) was highest in the middle-aged group. This suggests that although sleep

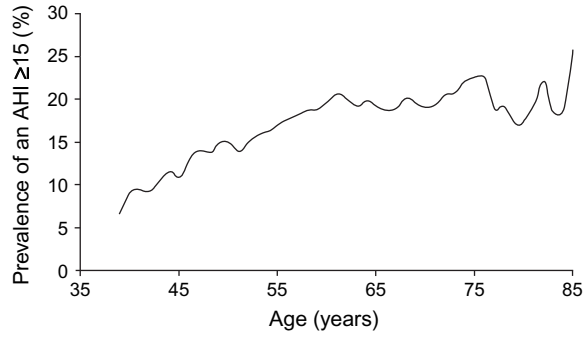

Figure 23.2. Prevalence of sleep apnea over five decades. Sleep apnea is defined as an apnea–hypopnea index >15. Plot is a 5-year moving average. Reprinted with permission from [11].

Table 23.1. Prevalence of sleep apnea in the elderly

Reference	Methodology	Sample size	Male:female	Age (years)	Results
[8]	Home PSG	145	68:77	≥65	AI ≥ 5 = 18%
[9]	Laboratory	105	49:56	60–91	AHI ≥ 5:
	PSG				60–69 = 2.9%
					70–79 = 33.3%
					80–91 = 39.5%
[10]	Home PSG	427	197:230	≥65	AI ≥ 5 = 24% RDI ≥ 10 = 62%
[11]	Home PSG	5615	2648:2967	40–98	AHI 5–14:
					39–49 = 19%
					50–59 = 24%
					60–69 = 32%
					70–79 = 33%
					80–99 = 36%
					AHI ≥15:
					39–49 = 10%
					50–59 = 16%
					60–69 = 19%
					70–79 = 21%
					80–99 = 20%

AHI, apnea–hypopnea index; AI, apnea index; PSG, polysomnography; RDI, respiratory disturbance index.

apnea is more prevalent in the elderly, it is less likely to be symptomatic and to have physiological consequences such as significant hypoxemia. This raises the issue of its clinical relevance and whether the criteria for diagnosis of sleep apnea should be different in the elderly than in middle-aged adults.

Pathogenesis of sleep apnea

The underlying mechanisms that promote the development of sleep apnea in the elderly can be classified into three broad categories, namely: (1) replication of the pathophysiology of sleep apnea in middle-aged adults; (2) physiological changes that are uniquely associated with aging; and (3) consequences of chronic medical disorders and/or medications.

Pathophysiology of sleep apnea in middle-aged adults

The predominant cause of obstructive sleep apnea in middle-aged adults is obesity, either through its effects on the pharynx and to a lesser extent on lung volume [13]. Although obesity is a strong predictor of sleep apnea in the elderly [10], it is not as strong as in younger subjects [11]. In the Sleep Heart Health Study the strength of the association between sleep apnea and body weight decreased as age increased. Male gender is a strong risk factor for sleep apnea, with males having approximately twice the prevalence of sleep apnea as females [11]. This increased prevalence in males is still seen in the elderly [9], despite the fact that after menopause the prevalence of sleep apnea increases significantly in women.

Physiological changes that are unique to aging

There are conflicting data on how aging affects the upper airway, the diameter of which has been reported to be larger [14, 15] or smaller [16, 17] in older adults compared to control subjects. Upper airway resistance has been found to be increased in the elderly in some studies [18] but not in others [19, 20]. Functionally, advancing age is associated with increased pharyngeal collapsibility and increased pharyngeal resistance during sleep [21], both of which may predispose to the pathogenesis of obstructive sleep apnea and contribute to an increased prevalence of obstructive sleep apnea in the elderly. This topic has been reviewed in greater detail in Chapter 7.

Since the prevalence of central sleep apnea appears to be increased in the elderly, it is possible that factors which promote the development of central apnea may be enhanced by aging. For example, an increased ventilatory response to hypercapnia can promote the development of sleep apnea by destabilizing the chemical control of breathing [22]. However, it appears that the ventilatory response to hypercapnia during euoxic wakefulness is not altered by aging. In fact, the sensitivity of the hypercapnic ventilatory response may be *reduced* during hypoxia in the elderly [23]. The change in the ventilatory response to hypercapnia during transition from wakefulness to sleep also influences the development of central sleep apnea. Normally, the hypercapnic ventilatory response is reduced during this transition, which helps to stabilize breathing during sleep. Loss of this stabilizing response during aging could promote the development of central apnea. The stability of the chemical control system during sleep can be assessed by measurement of the loop gain, which is defined as the ventilatory response to an initial respiratory perturbation [22]. However, comparison of loop gain in healthy young and elderly subjects found no significant difference between them [24]. Consequently there is no convincing evidence that aging per se destabilizes the control of breathing and, by implication, that age-related changes in the control of breathing are responsible for the increased prevalence of sleep apnea in the elderly. One limitation of these studies is that they were performed on healthy subjects without sleep apnea, which may have influenced the results.

Chronic medical disorders that are associated with sleep apnea

The prevalence of chronic medical disorders increases with advancing age and many of them, such as heart failure, stroke and renal failure, are associated with the development of sleep apnea. Consequently, it is possible that this changing demographic accounts for the increased prevalence of sleep apnea in the elderly. In a study of patients with congestive heart failure, which predominantly enrolled subjects over 65 years, 71% of those whose left ventricular ejection fraction was less than 40% had sleep apnea, defined as an AHI greater than 10 [25]. Forty-three percent of patients had OSA and 28% had Cheyne-Stokes respiration. Similarly, the prevalence of sleep apnea is high in patients who have suffered a stroke; in one recent study 53% of patients with an acute stroke had sleep apnea, reflected by an

Table 23.2. Central and obstructive sleep apnea in the elderly

	Age			
	20–44	45–64	65–100	Total
	(N = 236)	(N = 430)	(N = 75)	(N = 741)
Sleep apnea:	1.2 (0.4, 3.8)			
Obstructive	–	4.7 (3.1, 7.1)	1.7 (0.3, 9.1)	3.3 (2.2, 4.8)
Central		0.4 (0.1, 1.8)	1.1 (0.1, 8.9)	0.4 (0.1, 1.2)
Apnea/hypopnea index:	7.9 (5.0, 12.1)			
≥5	3.2 (1.6, 6.4)	19.7 (16.2, 23.7)	30.5 (21.1, 41.7)	17.0 (14.5, 19.9)
≥10	1.7 (0.6, 4.4)	11.8 (9.1, 15.3)	23.9 (15.7, 34.9)	10.5 (8.3, 12.7)
≥20		6.4 (4.3, 8.9)	13.3 (7.3, 23.0)	5.6 (4.0, 7.4)
Obstructive apnea/ hypopnea index:	7.9 (5.0, 12.1)			
≥5	3.2 (1.6, 6.4)	18.8 (15.4, 22.8)	24.8 (16.3, 35.7)	15.9 (13.5, 18.7)
≥10	1.7 (0.6, 4.4)	11.3 (8.5, 14.5)	18.1 (10.9, 28.4)	9.4 (7.4, 11.6)
≥20		6.3 (4.2, 8.8)	5.1 (1.9, 13.0)	4.7 (3.3, 6.3)
Central apnea index:	–			
≥2.5	–	1.7 (0.8, 3.4)	12.1 (6.5, 21.6)	2.2 (1.3, 3.5)
≥20		–	5.2 (2.0, 13.2)	0.5 (0.2, 1.4)

*Diagnosed in sleep disorders clinic.

All numbers are percentages.

The prevalence of sleep apnea, measured by apnea–hypopnea index, increases with age but central apnea accounts for a greater proportion of this increase than obstructive apnea.

Reprinted with permission from [12].

AHI greater than 10 [26]. In contrast to these results, one large community-based study found no association between a history of heart disease or stroke and sleep apnea in the elderly [10]. The prevalence of sleep apnea in end-stage renal disease has been reported to be at least 60% in middle-aged patients [27]. Consequently, the co-existence of chronic medical disorders in the elderly may contribute to an increased prevalence of sleep apnea in this patient population.

Clinical presentation of sleep apnea

Notwithstanding the fact that a significant proportion of elderly patients may have asymptomatic sleep apnea, those with symptoms can present in a variety of ways. Elderly patients with sleep apnea can present with typical clinical features such as snoring, choking or gasping respirations, witnessed apneas, morning headaches, hypertension, and daytime sleepiness [28, 29]. However, it is important to recognize that sleep apnea may also be heralded by atypical symptoms that are unique to this age group. Enuresis may be a consequence of sleep disordered breathing in the elderly [30], and can be improved with effective treatment of sleep apnea. Nocturnal wandering or confusion may be associated with sleep apnea [10]. Cognitive impairment, measured by Mini-Mental State Examination [31], delayed verbal recall, and impaired constructional abilities, and even dementia [32], have all been described in the elderly with sleep apnea. Falls during the day or night-time are associated with sleep disordered breathing [33], but more detailed studies are needed to further evaluate this association. Ocular conditions associated with OSA have also been described. These include glaucoma and non-arteritic anterior ischemic optic neuropathy (NAION) [34, 35].

In the middle-aged population, anthropomorphic features, such as body mass index (BMI), neck circumference and waist-to-hip ratio, and a history of snoring and nocturnal choking, are significantly associated with the AHI and, hence, are considered predictive of sleep apnea [36]. One study has demonstrated that these typical anthropomorphic features and symptoms are also predictive of sleep apnea in the elderly [28]. However, the Sleep Heart Health Study demonstrated that age modifies the relationship between body habitus and AHI. At age 40 the odds ratio for a positive association between BMI and AHI was 2.0 (1.7–2.4), but by age 80 it was 1.3 (1.1–1.5). Neck circumference was no longer a significant predictor of AHI by age 80 and waist-to-hip ratio was no longer significant by age 70. This suggests that anthropomorphic features used to predict sleep apnea in middle-aged subjects may not be as robust in the elderly. In addition, a history of snoring was noted to decrease 1.8-fold from age 50–60 to age 70 and beyond [11], indicating that typical symptoms of sleep apnea may not be reported as frequently in the elderly.

Diagnosis of sleep apnea

If sleep apnea is suspected, objective assessment of breathing during sleep is required both to confirm the diagnosis and determine its severity. Comprehensive overnight polysomnography in the sleep laboratory is the gold standard for the diagnosis of sleep disordered breathing [37]. Alternative diagnostic testing includes nocturnal cardiopulmonary monitoring (i.e. without sleep monitoring) and polysomnography at home. Unfortunately, studies that have evaluated these diagnostic modalities have not included elderly subjects, and consequently we are left to extrapolate from studies on younger subjects. Cardiopulmonary monitoring in middle-aged subjects has been found to be as effective as polysomnography in predicting which patients will benefit from continuous positive airway pressure (CPAP) therapy in terms of improved quality of life [38]. Furthermore, a recent randomized study of selected patients with a high probability of OSA compared cardiopulmonary monitoring with polysomnography in the diagnosis and treatment of sleep apnea and found no difference in their outcome measurements, which included AHI on CPAP, daytime sleepiness, quality of life, and CPAP requirement [39]. Although these data suggest that cardiopulmonary monitoring may be adequate to diagnose sleep apnea in selected elderly subjects, this needs to be confirmed by studies that are directed specifically at this patient population. This suggestion is supported by the fact that the elderly have some unique factors that may confound the accurate interpretation of limited diagnostic testing. For example, the high proportion of central apnea and increased prevalence of periodic limb movements in the elderly may require monitoring of respiratory effort and leg movements, respectively. If this type of monitoring is not available or reliable on an ambulatory system, full polysomnography may be required. Additionally, some elderly subjects are not capable of setting up a monitoring system at home either because of infirmity and/or lack of family support; in such cases, attended monitoring in a sleep laboratory may be the best option.

Impact of sleep apnea on clinical outcomes

Daytime function

Sleepiness

Sleep apnea is associated with increased daytime sleepiness in the elderly. In a cross-sectional study of elderly Japanese-American men, severe sleep apnea (AHI ≥30) was associated with daytime sleepiness as measured by the Epworth Sleepiness Scale [4]. Even mild sleep apnea in the elderly, as defined by an AHI ≥5, has been associated with increased daytime sleepiness compared to elderly patients with an AHI <5 [40]. In studies that have included elderly patients, treatment of OSA with CPAP can reduce daytime sleepiness as measured by ESS and improve daytime vigilance as measured by driving simulation performance [41, 42, 43].

Neurocognitive function

Neurocognitive function in the elderly may be influenced by multiple factors including age itself. Although sleep apnea may intuitively contribute to changes in neurocognitive function in the elderly, studies to date have shown conflicting evidence. In a 3-year follow-up study of randomly selected elderly patients there was no difference in neuropsychiatric or medical outcomes in subjects with mild or moderate OSA compared to healthy controls [44]. Vigilance testing on community-dwelling elderly volunteers using a simulated driving test has shown that vigilance is not significantly decreased by sleep apnea syndrome; however, decreased vigilance is associated with increasing age

[45]. In contrast, other studies have demonstrated decreased performance on the Mini-Mental Status Examination associated with increased daytime sleepiness and the severity of sleep apnea reflected by the RDI [31]. Furthermore, the impact of sleep apnea on daytime function can be amplified by co-existing sleep disorders such as insomnia [28].

Diminished neurocognitive performance associated with sleep apnea in the elderly may be due to intermittent nocturnal hypoxia (executive and psychomotor function) [46, 47, 48] or excessive daytime sleepiness and reduced vigilance as a result of sleep fragmentation (attention and memory) [31, 49, 50, 51] or both [52]. In the elderly with mild sleep apnea, increased AHI is associated with greater memory impairment in APOE epsilon4 carriers than non-carriers [53]. The APOE epsilon4 allele is a genetic risk factor that increases the risk of cognitive deterioration, both the development of Alzheimer's disease and cognitive decline in non-demented older adults, in the presence of other modifying factors such as sleep apnea.

Treatment of sleep apnea with CPAP has been shown to improve cognition in the elderly. In 12 sleep apnea patients over 55 years of age, baseline RDI and oxygen desaturation were associated with impaired neurocognitive function. Treatment of sleep apnea with CPAP for 3 months showed greater improvement in attention, psychomotor speed, executive functioning, and non-verbal delayed recall in those who were compliant with CPAP [32]. Therapeutic CPAP also improved steering performance and reaction time to target stimuli in patients with OSA [42].

Mood

There is a dose–response relationship in the elderly between OSA and the risk of developing depression [54]. Furthermore, in post-stroke patients, OSA is associated with delirium, depression, increased latency in response to verbal stimuli, and poorer performance of activities of daily living [55]. Whether treatment of sleep apnea improves symptoms of depression in the elderly is unclear.

Cardiovascular disease

Hypertension

Obstructive sleep apnea is associated with hypertension in the elderly. In a 1-year follow-up of elderly patients, those with sleep apnea (apnea index ≥5) had higher systolic blood pressure than those without sleep apnea [56]. Although CPAP therapy has been found in a recent meta-analysis to significantly improve blood pressure, randomized controlled trials of CPAP therapy to date have not included elderly subjects [57].

Coronary artery disease

Sleep apnea has been shown to be modestly associated with cardiovascular disease in the Sleep Heart Health Study [58]. Because of its association with hypertension, sleep apnea is felt to play a role in cardiovascular disease risk. Whether treatment of sleep apnea in the elderly decreases the risk of cardiovascular disease has not been specifically addressed.

Congestive heart failure

In the Sleep Heart Health Study, which included elderly subjects, OSA was also associated with an increased risk of congestive heart failure with an odds ratio of 2.38 independent of other known risk factors [58]. Congestive heart failure is also a significant risk factor for the development of central sleep apnea, and sleep apnea is present in about 30–40% of patients with congestive heart failure [59, 60].

Stroke

Severe sleep apnea (AHI ≥30) is associated with an increased risk of stroke in the elderly with an adjusted hazard ratio of 2.52 [61]. Furthermore, intolerance of CPAP in a group of elderly patients with OSA following stroke increased the probability of a new vascular event five-fold (odds ratio 5.09) even after adjusting for other vascular and neurological risk factors [62]. It is not known whether treatment of sleep apnea with CPAP decreases the risk of stroke in the elderly before a cerebrovascular event.

Mortality

There is conflicting evidence as to whether sleep apnea increases mortality in the elderly. In a 10-year follow-up of community-dwelling elderly, subjects with a respiratory disturbance index ≥30 had a shorter survival but sleep apnea was not an independent predictor of death (age and cardiovascular and pulmonary disease were identified as independent predictors) [63]. Evaluation of a sleep clinic population showed that severe OSA (AHI >30) was associated with increased mortality but this effect was limited to subjects who were less than 50 years [64]. These findings may reflect a survival bias, which could mask a significant association

between sleep apnea and increased mortality in the elderly. Finally, investigation of nursing home residents showed that elderly women with an AHI ≥5 had significantly increased mortality [65]. This effect may be amplified by co-morbid disease as suggested by the findings of a long-term follow-up study in which the presence of central sleep apnea was associated with a shortened lifespan in elderly subjects with congestive heart failure (HR 1.66, p = 0.012) [66].

Treatment of sleep apnea

Obstructive sleep apnea

Conservative measures that are used to treat sleep apnea in younger adults should also be considered in the elderly patient. After the identification and treatment of any underlying medical disorders that contribute to sleep apnea, such as hypothyroidism and acromegaly, weight reduction, the avoidance of alcohol and sedative/hypnotic medication close to bedtime, and postural therapy can be considered.

Continuous positive airway pressure is the gold-standard therapy for OSA[67] and it has been shown to be effective in the elderly [41]. Elderly patients generally require lower CPAP levels than weight-matched younger subjects, which probably reflects differences in the compliance of the elderly pharynx that has been previously outlined [62]. Compliance with CPAP therapy in the elderly is correlated with attendance at a CPAP education class and improvement of daytime symptoms. Compliance is negatively correlated with nocturia and benign prostatic hypertrophy [68]. Treatment of sleep apnea with CPAP is feasible in the elderly with mild to moderate dementia. Continuous positive airway pressure adherence in community-dwelling patients with Alzheimer's disease averaged 4.8 hours/night. Depressive symptoms predict lack of compliance in this group [69].

Oral appliances can be used as an alternative to CPAP in middle-aged patients with mild OSA [70], although the use of these appliances may be limited in older patients by poor dentition.

In the absence of correcting a specific upper airway abnormality, such as enlarged tonsils, surgical therapy has a very limited role for the management of sleep apnea in adults. This role is even more limited in the elderly where abnormalities such as enlarged tonsils are a rarity and co-existing medical disorders increase the risk of surgical procedures. Although upper airway surgery such as uvulopalatopharyngoplasty and laser-assisted uvuloplasty have been extensively used to treat sleep apnea, its efficacy for correcting sleep apnea is small [67] and its efficacy in the elderly has not been specifically examined since most studies have excluded patients over 65 years [71].

In the middle-aged population with sleep apnea, pharmacological management of residual daytime sleepiness following CPAP therapy with modafinil has been shown to be beneficial [72, 73], but this has not specifically been examined in the elderly.

Central sleep apnea

Although the treatment of central sleep apnea is challenging in all age groups, including the elderly, several options may be considered. The decision to treat sleep apnea is mainly determined by the presence of associated nocturnal or daytime symptoms as there is no convincing evidence that treatment of central apnea confers a survival benefit. The specific therapy chosen needs to be individualized for each patient and depends partly upon the underlying cause of sleep apnea. Cheyne-Stokes respiration (CSR) can be corrected by improvement of ventricular function in patients with congestive heart failure [74]. Alternative therapeutic interventions for central sleep apnea, including CSR, include supplemental oxygen [75, 76, 77], which is not universally effective, and inhaled carbon dioxide [78, 79], which has been demonstrated to be effective in the sleep laboratory but is not a feasible long-term option at the present time. Short-term use of respiratory stimulants, such as theophylline and acetazolamide, has also been demonstrated to improve CSR severity and acetazolamide was also demonstrated to improve daytime symptoms in patients with heart failure [80, 81]. A prospective randomized controlled trial of CPAP in patients under 65 years of age with congestive heart failure and CSR found that CPAP reduced apnea, improved nocturnal oxygenation, the 6-minute walk test, and ejection fraction but did not confer a survival benefit [82]. A subsequent post hoc analysis of data from this study reported that CPAP did improve survival in patients whose sleep apnea improved, which was defined as a reduction in AHI to less than 15 [83]. For elderly patients with CSR and heart failure, adaptive servoventilation (ASV) improves AHI and daytime sleepiness [84]. In a study of middle-aged and elderly patients with complex sleep apnea (persistent CSA despite CPAP treatment of OSA), non-invasive positive pressure ventilation (NIPPV) and ASV improved AHI [85].

Summary

Sleep apnea is common in the elderly. Its multi-factorial etiology results in a more heterogeneous clinical and polysomnographic presentation than what is characteristically seen in younger adults. Furthermore, the elderly present some unique challenges for the diagnosis and treatment of sleep apnea, which may require modification of the diagnostic algorithms that have been established in middle-aged patients. Although there is evidence that untreated sleep apnea has clinical consequences, more research that is specifically directed at this patient population is required to determine its impact on important clinical outcomes and co-morbid disease. The need for this direction is likely to grow as the population ages and the associated prevalence of sleep apnea increases.

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Part 3
Chapter
24

Sleep disorders in the elderly

Sleep and cardiovascular diseases in the elderly

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Introduction

Sleep has been ascribed a restorative function for the body and mind, and is pivotal for maintenance of normal health. Sleep disorders are common in the elderly with a symptom prevalence rate approaching 50% in elderly community populations [1]. Cardiovascular disease is the leading cause of death in the elderly as well as for all adults over age 35 years [2]. Therefore, it is not surprising that diverse physiological and pathological changes associated with sleep may contribute to cardiovascular morbidity, particularly with increasing age. Variability in autonomic activity during different sleep stages leads to changes in cardiac output, blood pressure, and heart rate. This may tax the cardiovascular system and be conducive to augmented morbidity and mortality. The incidence of adverse cardiovascular events is particularly elevated during the early morning hours (06:00 to 12:00). Up to 20% of myocardial infarctions and 15% of sudden cardiac deaths may be sleep related. Habitual snoring, a form of sleep disordered breathing (SDB, see below), has been demonstrated to be a risk factor for early morning cardiovascular deaths [3]. Moreover, daytime sleepiness is associated with cardiovascular morbidity and mortality in older adults, especially in older women [4].

Obstructive sleep apnea (OSA), a frequent form of SDB, is associated with commonly occurring cardiovascular disorders, including hypertension, coronary artery disease, congestive heart failure (CHF), arrhythmias, and stroke [5]. The concordance of OSA and cardiovascular disorders is independent of obesity and other cardiovascular disease risk factors [6]. The association between OSA and hypertension has been observed in a number of both cross-sectional and longitudinal studies [7]. However, this relationship may be much weaker in the elderly [7]. Less robust data are available to support the association between OSA and coronary artery disease or stroke. Central sleep apnea (CSA) is frequently associated with CHF. Cheyne-Stokes respiration (CSR), a form of periodic breathing, commonly accompanies CSA patients with heart failure and portends increased mortality. The information that follows in this chapter will explore these and other associations between sleep disorders and cardiovascular disease in more detail.

Normal sleep and cardiovascular physiology

Sleep is associated with recurrent fluctuations in autonomic activity, and consequently may impose a burden on the cardiovascular system. Non-rapid eye movement (NREM) sleep is a state of relative autonomic stability. There is increased baroreflex sensitivity and vagal predominance resulting in a tendency towards a lower heart rate and arterial blood pressure. With aging there is a loss of heart rate variability (HRV), especially the component related to vagal or parasympathetic activity [8]. In younger people, men have greater HRV than women. While some studies have suggested that this gender difference is not observed in the elderly, these studies had a small number of subjects. In the Cardiovascular Health Study, where HRV was measured in 1273 adults 65 years and older, significant gender difference in HRV was observed, emphasizing the importance of performing larger studies in the elderly [8]. In contrast to decreasing parasympathetic activity, the activity of the sympathetic nervous system may be increased in both younger persons as well as the elderly. In addition, rapid eye movement (REM) sleep is associated with surges in sympathetic activity, suppression of vagal tone, and disruption of cardiovascular homeostasis. Sympathetic nerve activity during REM sleep may be higher than that during wakefulness and can result in pronounced elevations in heart rate and blood pressure. Muscle sympathetic nerve activity may decrease with transient increases in muscle tone during REM and result in reduced heart rate and blood pressure. In

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contrast, arousals from NREM sleep may result in increased muscle sympathetic nerve activity, accompanied by increases in heart rate and blood pressure. The fluctuations in venous return, cardiac output, peripheral vascular resistance, heart rate, and blood pressure are a potential mechanism that can contribute to the development of adverse cardiovascular events during sleep.

Sleep disordered breathing

Sleep disordered breathing refers to a spectrum of disorders including snoring, OSA, CSA, and upper airway resistance syndrome. Sleep disordered breathing is highly prevalent in the elderly and the odds of having significant SDB are estimated at 1.79 per 10-year increase in age [9]. The apneas in the elderly may consist of various combinations of central, mixed, or obstructive events [10].

Sleep disordered breathing and hypertension

The relationship between OSA and hypertension was first described in a subject undergoing tracheostomy, which was followed by an unexpected decrease in systemic blood pressure [11]. Since then many epidemiological and clinic-based studies have confirmed the association between SDB and hypertension [12, 13]. These associations have been more thoroughly evaluated for OSA than CSA. While there are relatively few studies looking at this relationship in elderly populations, some of the large trials included subjects who were middle-aged or elderly.

In the Outcomes of Sleep Disorders in Older Men Sleep Study, polysomnographic SDB in 2911 elderly men was associated with hypertension (odds ratio (OR) = 1.26, 95% CI = 1.06–1.50) [12]. Another study found the Epworth Sleepiness Score (ESS), a measure of subjective daytime sleepiness highly correlated with SDB, to be an individual risk factor for hypertension in a group of 157 healthy men and women 55–80 years of age [13].

However, not all community-based studies have detected a relationship between SDB and hypertension in elderly persons. The Sleep Heart Health Study is a large, prospective, multi-center community-based cohort study aimed at elucidating the cardiovascular and other consequences of sleep-disordered breathing. Cross-sectional analyses from these data demonstrated a significant increase in the prevalence of hypertension with increasing SDB measures [7]. Notably, 46.7% of the subjects in this study were ≥65 years of age. The odds ratio for the presence of hypertension in the highest category of AHI (30 per hour) compared with that in the lowest category (<1.5 per hour) was 1.37 after adjusting for confounding factors such as age, sex, body mass index (BMI), waist and neck circumference, and presence of baseline hypertension. However, this observation was not evident among those over the age of 65 years [7]. A similar lack of association between hypertension and snoring was noted in the Cardiovascular Health Study, a multi-center prospective cohort study of elderly persons [14].

In contrast to community-based studies, the association between OSA and hypertension has been confirmed in clinic settings. In a study of late middle-aged patients (57.2 ± 1.6 years) with drug-resistant hypertension (taking, on average, 3.6 different antihypertensive medications daily) seen in a hypertension clinic, 83% had OSA, defined as an AHI >10/hour [15]. Another study of late middle-aged patients (57.2 ± 9 years) with sleep apnea seen at a sleep disorders center and using regular antihypertensive medications for more than 6 months found that the patients with poorly controlled hypertension had a higher mean AHI than those whose hypertension had been optimally controlled [16]. In one study of 150 elderly veterans presenting at Veterans Administrations hypertension clinic, those with hypertension, despite treatment, had significantly worse SDB than subjects with normotensive blood pressure values [17].

Blood pressure (BP) usually fluctuates in a diurnal manner with the average night-time BP frequently dipping to values 10–20% lower than their average daytime BP. Non-dipping refers to absence or blunting of this expected decrease in blood pressure and occurs in as many as 25% of individuals with essential hypertension. The odds of non-dipping increase with age and are approximately six times higher in persons 60–80 years old compared to those 20–30 years of age. The phenomenon of non-dipping is associated with a higher risk of hypertensive complications including left ventricular hypertrophy, stroke, microalbuminuria, and retinopathy. Obstructive sleep apnea patients have a higher prevalence of non-dipping compared to controls without OSA and has been hypothesized to be related to the decrement in quality of sleep resulting from recurrent apneas and arousals.

Clinical trials generally have demonstrated a modest decrease in BP with continuous positive airway

pressure (CPAP) therapy for OSA. In a recent meta-analysis of 16 studies representing 818 participants, mean net changes in systolic, diastolic, and mean blood pressure after CPAP in comparison to controls were: –2.46 mmHg (95% CI –4.31 to –0.62); –1.83 mmHg (95% CI –3.05 to –0.61); and –2.22 mmHg (95% CI –4.38 to –0.05), respectively. One retrospective study observed an 11.2 mmHg drop in systolic blood pressure and a 5.9 mmHg drop in diastolic blood pressure with an average 12.1 months of use in hypertensive, but not normotensive, patients with OSA [18]. The mean age of the hypertensive patients was 57 years. However, most studies report a more modest decrease in blood pressure, in the range of 1–5 mmHg. One small study of 11 patients aged 57 ± 2 years also demonstrated attenuation of hypertension with regular CPAP use in patients with refractory hypertension (poorly controlled hypertension despite daily use of three or more types of antihypertensive medications) and co-existent OSA [15].

Therapeutic modalities for OSA other than CPAP for treatment have also demonstrated a reduction in blood pressure. These include mandibular advancement splint and otolaryngological surgery. One study found improvement in blood pressure in proportion to the oxygen desaturation time, but not AHI, in 65 patients with OSA after surgery [19]. This suggests that hypoxemia rather than obstruction per se may be the sentinel factor in elevation of blood pressure.

The trials assessing the impact of treatment of OSA on hypertension primarily in elderly subjects have demonstrated variable results, with some studies reporting alleviation of hypertension and other studies showing no effect compared to placebo [20]. Several factors such as small sample sizes, lack of a consistent definition for apneas and hypopneas, lack of proper randomization, inadequate blinding, short follow-up duration, and inclusion of both hypertensive and normotensive subjects may contribute to variable results seen in these studies. Some studies have looked at the subjective parameters of sleepiness and suggest that CPAP may have mitigating effects on hypertension only in persons who have daytime sleepiness [21]. This finding, if confirmed in larger trials, may have a bearing on the treatment of hypertension in the elderly, who have been shown to have less daytime sleepiness than younger patients.

In conclusion, there is a strong association between OSA and hypertension. However, whether the therapy of OSA in elderly patients attenuates hypertension is yet to be clearly elucidated. We recommend treating hypertension in elderly OSA patients with antihypertensive medications. If the patient is significantly hypoxic, has severe OSA, daytime symptoms from OSA, or has hypertension resistant to medical therapy, treatment of OSA should be strongly considered. Furthermore, elderly hypertensives resistant to standard antihypertensive therapy may require evaluation for the presence of OSA.

Sleep disordered breathing and ischemic heart disease

There is increasing evidence of an association between sleep disorders, especially OSA, and ischemic heart disease (IHD), but the current evidence is not as robust as that for the association between OSA and hypertension. Furthermore, data specific to elderly populations are relatively sparse. In one study of 5201 older adults, self-reported sleep disturbances were associated with a higher prevalence of angina [22]. More recently, in the Outcomes of Sleep Disorders in Older Men Sleep Study, polysomnographic SDB was associated with prevalent cardiovascular disease (OR = 1.24, 95% CI 1.19–1.29) [12]. A cross-sectional analysis of data from the Sleep Heart Health Study involving older patients (mean age for all groups >60 years) showed a dose–response relationship between severity of OSA and prevalence of coronary heart disease and heart failure [23]. One prospective study of 182 middle-aged men found a higher incidence of cardiovascular disease in those with OSA than those without (37% vs. 7%) [24]. Patients 70 years and younger with known coronary artery disease who have OSA have worse long-term prognosis than those with coronary artery disease but without OSA [25]. Cardiovascular mortality is also increased in patients with OSA. A prospective study of late middle-aged patients (57.3 ± 10.1 years) with angiographically proven coronary artery disease (CAD) and polysomnographically determined OSA revealed a much higher incidence (58% vs. 24%) of cardiovascular death, acute coronary syndrome, hospitalization for heart failure, or need for coronary revascularization in subjects who declined OSA treatment compared to those treated with CPAP or upper airway surgery. This study also showed a higher incidence of cardiovascular disease events in those whose OSA was inadequately treated compared to those with optimum treatment. Whether these observations hold true for elderly patients, however, is unclear.

OSA is also associated with worse outcomes in patients with acute coronary syndrome after percutaneous coronary intervention (PCI). One study followed 89 older patients (20 women, 69 men; mean age 66 ± 11 years) with acute coronary syndrome who were successfully treated with PCI and were followed for a mean period of 227 days [26]. All patients underwent quantitative coronary angiography at 6-months follow-up, wherein minimum luminal diameter, reference segment diameter, and percent diameter stenosis at end-diastole were assessed. The follow-up angiography depicted significantly greater late loss and a higher binary re-stenosis rate in patients with OSA compared with those without OSA. Furthermore, the rates of major adverse cardiac events including revascularizations and cardiac mortality were significantly higher in patients with OSA. Another study of 86 older patients (mean age 68 years) involving PCI for acute myocardial infarction (MI) found that the increases in left ventricular ejection fraction and regional wall motion within the infarct area 21 days after PCI were significantly lower in OSA patients than those without OSA [27]. While there are data to suggest alleviation of cardiovascular morbidity and mortality in younger patients with treatment of OSA, such data in elderly patients are meager.

In conclusion, some recent studies corroborate the causal role of OSA in the genesis or progression of IHD. There is less data in elderly patients regarding the beneficial impact of OSA therapy on improvement of cardiovascular morbidity.

Sleep disordered breathing, hypertension, and ischemic heart disease: pathogenesis

Obstructive sleep apnea, the most common type of sleep apnea, is characterized by recurrent partial or complete obstruction of upper airway resulting in hypopneas or apneas, respectively. The episodes of upper airway collapse lead to increased respiratory efforts and repetitive large negative intrathoracic pressure swings. The latter produce significant increases in the left ventricular transmural pressure gradient, leading to an augmentation of the preload and the afterload. Chronic intermittent hypoxia from episodic airway collapse is associated with autonomic activation of the sympathetic system. Arousals, which generally terminate obstructive events, also contribute to sympathetic activation. The increased stress on the heart from an increased mechanical load as well as post-apneic autonomic perturbations can contribute to adverse cardiac sequelae. Hypoxemia, however, appears to be the primary mechanism whereby OSA produces its deleterious cardiovascular effects, and its impact may be dose dependent. Obstructive sleep apnea patients with worse nocturnal hypoxemia appear to have higher odds of developing hypertension [7]. Severe nocturnal hypoxemia, rather than the number of apneic and hypopneic episodes or apnea–hypopnea index (AHI), has also been demonstrated to be the strongest independent predictor of left ventricular hypertrophy in OSA [28]. Hypoxemia also leads to increased reactive oxygen species (ROS) generation, increased sympathetic activity, inflammation, increased levels of adhesion molecules, endothelial injury, release of potent vasoconstrictor endothelin, and impaired baroreflex sensitivity. Repetitive hypoxemia significantly correlates with levels of tissue factor, a sentinel molecule in the clotting cascade. Finally, the episodic nocturnal oxygen desaturations may lead to recurrent cardiac ischemia and contribute to ischemic heart disease and arrhythmias.

The hypoxia-reoxygenation resulting from intermittent airway obstruction is associated with ROS generation and oxidative stress. The increased sympathetic activity itself can contribute to the ROS generation. There is increased production of free radicals from monocytes and neutrophils in OSA, providing direct evidence of oxidative burden. Other markers of oxidative stress such as lipid peroxidation, release of superoxide from polymorphonuclear neutrophils, 8-isoprostane levels, malondialdehyde levels, and urinary 8-hydroxy-2'-deoxyguanosine excretion are also increased in OSA. Furthermore, HDL, an antiatherogenic molecule with antioxidant properties, is dysfunctional in patients with OSA, which may prevent the inactivation of oxidized lipids and may contribute to the increased cardiovascular risk [29]. Antioxidant vitamin C improves endothelial function in OSA, further corroborating the role of oxidative stress in effecting endothelial dysfunction. Oxidative stress plays a role in various cardiovascular disorders such as atherosclerosis, ischemic heart disease, and hypertension. Some of these effects may be mediated by peroxynitrite, a result of a combination of oxygen free radicals with nitric oxide. Peroxynitrite inhibits the vasodilator, antiproliferative, and antithrombotic effects of prostaglandin I_2 and stimulates the potent vasoconstrictive, proliferative, and prothrombotic effects of prostaglandin H_2 [30]. Notably,

the levels of free oxygen radicals and products of lipid peroxidation attenuate with the use of positive airway pressure (PAP) therapy for OSA.

OSA is also characterized by local and systemic inflammation. Patients with OSA have increased levels of interleukin (IL)-6, soluble IL-6 receptors, IL-18, C-reactive protein (CRP), and tumor necrosis factor-alpha (TNF-alpha) when compared to matched obese control subjects [31, 32]. The activity of transcription factor nuclear factor kappa B (NF-κB), the principal initiator of the inflammatory cascade, and the levels of NF-κB-dependent genes are also increased in OSA. Inflammation has been hypothesized to play an integral role in the pathogenesis of atherosclerosis. Indeed, the levels of IL-6, CRP, ESR, TNF-α, and P-selectin are increased in atherosclerotic conditions.

The oxidative stress as well as inflammation may result in endothelial injury. Endothelial dysfunction has recently been recognized as a likely link between SDB and cardiovascular disorders [32]. The normal endothelium is a source of vasodilating and antiproliferating compounds such as prostacyclin and nitric oxide. The injury to endothelium is characterized by decreased levels of these mediators as well as increased levels of the vasoconstricting endothelin-1 and thromboxane. Furthermore, endothelial dysfunction results in increased adhesion molecules such as intracellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and E-selectin, and contributes to increased coagulability and thrombogenecity. Finally, the normal endothelium secretes factors such as nitric oxide, prostacyclin, thrombomodulin, and heparin sulfates, which are antiaggregating and antithrombotic and help maintain normal fluidity of the blood. Endothelial dysfunction promotes platelet aggregation and plasma coagulation, and may play a central role in the development of disorders such as atherosclerosis.

Obstructive sleep apnea is a state of sympathetic overdrive. Autonomic perturbations characterized by sympathetic overactivity and depressed baroreflex control of heart rate during sleep have been frequently reported in OSA and are related to repeated arousals and intermittent hypoxemia. Sympathetic activity is increased in OSA patients during wakefulness and further increases during sleep. Presence of hypertension and OSA is characterized by more severe sympathetic activation and autonomic imbalance perturbations than hypertension without OSA. Catecholamine levels are also elevated in OSA. Treatment of OSA results in attenuation of sympathetic activity, decrease in catecholamine levels, and improvement in baroreflex sensitivity.

Furthermore, obesity and metabolic dysregulation are common features of OSA and likely contribute to cardiovascular consequences. Cross-sectional data from large population studies (the Sleep Heart Health Study and the Wisconsin Sleep Cohort) have demonstrated insulin resistance in patients with OSA. Similar results have been shown in clinical patients with OSA. The etiology of disturbed glucose metabolism in OSA is yet to be clearly elucidated, but may include sympathetic activation or inflammation triggered by intermittent hypoxemia and sleep fragmentation. The metabolic derangements in SDB are described in detail elsewhere in this book.

Cyclical variation in cerebral blood flow occurs with apneas [33]. Apart from the other derangements noted above, this may be another factor that confers an increased risk of strokes in patients with sleep apnea. Serum levels of soluble CD40 ligand and soluble P-selectin, proteins with a role in platelet activation and associated with an increased risk of cerebrovascular disease, are significantly higher in patients with moderate to severe OSA than in obese control subjects.

It is likely that many of the derangements described above including oxidative stress, inflammation, and endothelial dysfunction may be seen not only in OSA, but also in CSA. However, the presence of these derangements has been less well studied in CSA. Neurohormonal activation has been described in heart failure patients with CSA, and may contribute to the worse cardiac morbidity as well as increased mortality.

Genetic factors may modify the individual susceptibility of OSA patients to develop cardiovascular morbidity. There is an increased prevalence of the TNF-α (–308A) allele in patients with OSA, which contributes to overproduction of TNF-α compared to normal controls [34]. Tumor necrosis factor-alpha may play a role in atherogenesis. Another gene polymorphism noted in some patients with OSA is the presence of the D-allele of the angiotensin-converting enzyme (ACE) gene, which is associated with higher plasma ACE activity and forebodes an increased risk of hypertension [35]. A recent study has shown increased mRNA transcripts of antioxidant genes such as catalase and superoxide dismutase-2 in patients with OSA, probably an adaptive protective response against the increase in ROS.

In conclusion, there are a number of potential mechanisms that would explain associations between SDB, and hypertension and IHD. Whether these mechanisms are differentially operative in the elderly with SDB in comparison to younger persons with SDB is not certain.

Sleep disordered breathing and congestive heart failure

OSA and CSA are frequently encountered in patients with heart failure (HF) and contribute to mortality. One study of 700 patients with symptomatic CHF found SDB in 76% of the patients (40% CSA, 36% OSA) [36]. However, it is difficult to differentiate patients who have SDB from those who do not by symptoms or by routine cardiac assessment. In patients with heart failure, the predominant apnea type can shift from obstructive to central overnight and may be associated with a reduction in $PaCO_2$ and increase in lung-chemoreceptor circulation time.

Sleep disorder-related autonomic alterations may contribute to the adverse prognosis in these patients. Heart rate variability (HRV), a surrogate marker of the autonomic nervous system stability, is reduced in CHF patients with SDB and correlates with AHI and the oxygen desaturation index. A low HRV is also associated with worse survival. A recent study including elderly patients with CHF found that the median survival of patients with CSA (mean age 67 years) was 45 months compared with 90 months in those without CSA (mean age 62 years) (hazard ratio = 2.14, p = 0.02). [37]. The effect of CSA on survival was maintained after adjusting for left ventricular ejection fraction (LVEF), New York Heart Association (NYHA) functional class, heart rate, serum digoxin and sodium concentration, hemoglobin, and age.

A low $PaCO_2$ has been suggested to be the triggering factor for CSA in CHF patients. A higher left ventricular filling pressure and resultant pulmonary congestion may trigger stimulation of pulmonary vagal afferents, leading to tachypnea and hypocapnia. Central sleep apnea is frequently accompanied by Cheyne-Stokes respiration (CSA-CSR). The latter refers to a periodic breathing pattern whereby the tidal volumes increase and decrease alternately in a sinusoidal fashion. The oscillations in respiration are accompanied by cyclical changes in oxygen saturation, heart rate, and blood pressure, likely by modulation of the autonomic nervous system activity. Sympathomimetic activation may contribute to the increased mortality seen in CHF patients with CSA-CSR in comparison to those with comparable cardiac dysfunction, but without this abnormal breathing pattern. CSA-CSR may also promote ventricular irritability, thus facilitating the occurrence of arrhythmias. Use of adaptive servoventilation to treat CSR improves excessive daytime sleepiness and attenuates neurohormonal activation in patients with chronic heart failure. Treatment of CSR also improves exercise capacity and quality of life.

Obstructive sleep apnea is also associated with both systolic and diastolic heart failure and may be a cause or consequence of CHF. Several studies have shown ventricular (LV) hypertrophy in OSA and regression of cardiac hypertrophy with use of positive airway pressure (PAP) therapy. Multiple echocardiographic abnormalities, including left atrial enlargement, right atrial enlargement, and right ventricular hypertrophy have also been described in patients with OSA [38, 39]. One study of 40 patients with CHF and OSA (19 patients on CPAP therapy and 21 controls) found that CPAP use improved left ventricular ejection fraction and quality of life and decreased overnight urinary norepinephrine excretion. Left ventricular diastolic dysfunction also improves with treatment of OSA [38, 39].

Prevalence of CSA and OSA is also high in heart failure patients requiring cardiac transplants. One study of heart transplantation patients over 54 years of age reported significant improvement in sleep quality after transplant. Treatment of CHF patients with left ventricular or biventricular pacing decreases central apneas and improves sleep quality. Treatment of CSA in CHF patients with oxygen alone may stabilize sleep disordered breathing but CPAP has the added effect of significantly improving left ventricular ejection fraction and ventilatory efficiency during exercise in these patients.

The Canadian Continuous Airway Pressure for Patients with Central Sleep Apnea and Heart Failure (CANPAP) Trial was designed to assess the effect of CPAP on mortality in CHF patients with CSA [40]. This trial randomized 258 heart failure patients (mean age 63 ± 10 years) with CSA to either CPAP therapy (N = 130) or to the control group (N = 128). The use of CPAP therapy improved nocturnal oxygenation, increased the ejection fraction, lowered norepinephrine levels, and increased the distance walked in 6 minutes but had no effect on heart transplant-free

survival. However, CPAP only reduced the mean AHI to 19. A post hoc analysis of the subgroup of patients who had a PSG 3 months later revealed that the subjects whose AHI had been reduced to under 15, but not those whose AHI was higher than 15 despite regular CPAP use, did demonstrate a greater increase in left ventricular ejection fraction at 3 months (P = 0.001) and significantly better transplant-free survival (hazard ratio 0.371, P = 0.043) than control subjects.

Sleep disordered breathing and arrhythmias

The different sleep stages are associated with pronounced alterations in cardiac rate. During NREM sleep, an augmentation of parasympathetic activity with sympathetic activity persisting at levels similar to that during relaxed wakefulness leads to a relative predominance of parasympathetic drive. Rapid eye movement sleep is characterized by striking autonomic instability and variable heart rate. The sympathetic activity declines during tonic REM and leads to an imbalance in favor of parasympathetic activity. In contrast, during phasic REM, there is an upsurge in both sympathetic and parasympathetic activity, but sympathetic activity predominates. Consequently, there is cardiac acceleration during phasic REM and deceleration in tonic REM.

The profound vagal activation during NREM sleep may induce bradycardia and hypotension, leading to myocardial ischemia, and thence, arrhythmias. However, the autonomic fluctuations during REM sleep make it a more likely sleep stage for induction of arrhythmias. The augmented sympathetic activity facilitates arrhythmogenesis, especially in ischemic myocardium, which provides a favorable substrate for anomalous rhythm generation and conduction. Rapid eye movement sleep-related sinus arrest may occur secondary to abnormal vagal tone and may be an etiological factor for sudden death during sleep. Sinus pauses, however, occur less frequently in those over 80 years of age.

An assortment of cardiac arrhythmias, both atrial and ventricular, has been described in patients with OSA. Hypoxia associated with apneas, catecholamine fluctuations, alterations in intrathoracic pressure, and the related changes in left atrial stretch and variability in heart rate and cardiac output facilitate occurrence of arrhythmias. Exaggerated sinus arrhythmia is a frequent attendant of OSA. There is an association between minimum nocturnal arterial oxygen saturation and occurrence of nocturnal sinus bradycardia and supraventricular arrhythmias in OSA. Notably, the frequency of arrhythmias increases with increased severity of OSA, arrhythmias being uncommon in mild OSA. One study evaluated the prevalence of rhythm disturbances in 23 patients (50 ± 11 years old) with moderate to severe OSA with no known cardiac or sinus node dysfunction over a 14-month period – the first 2 months without CPAP therapy, and for 12 months after being initiated on CPAP using a subcutaneously implanted loop recorder. Almost half the patients had severe, primarily nocturnal arrhythmias prior to CPAP therapy, but the occurrence decreased significantly within 8 weeks of CPAP use, with no ectopy recorded during the second half of follow-up. Bradycardia and sinus pauses were recorded significantly more frequently than tachyarrhythmias.

Arrhythmias also occur more commonly in patients with CSA-CSR. Increased sympathetic activity seen in CSR may lead to excitation of the AV node, facilitate AV conduction, and increase ventricular irritability. Ventricular premature beats are commonly seen in patients with CSA-CSR, especially during the hyperpneic phase of the CSR. This is the phase during which sympathetic activation and chemostimulation are expected to peak, suggesting the breathing pattern to be a likely factor in the etiopathogenesis of ectopy.

Despite the association between SDB and arrhythmias, evidence suggests that this linkage is weaker in the elderly than in younger persons. In a recent study, age was not a factor predicting incident atrial fibrillation in persons with SDB over age 65 years, whereas it was significant in younger persons [41]. Furthermore, in the Sleep Heart Health Study the association between SDB and arrhythmias also was stronger in younger persons [42].

Sleep disordered breathing and stroke

A high prevalence of SDB including OSA is observed in stroke victims. The relationship between stroke and OSA appears to be bi-directional. The intima-media thickness of the carotid arteries and carotid-femoral pulse wave velocity, indicators of atherosclerosis, are increased in patients with OSA. In addition to increased carotid plaques, serum levels of inflammatory markers including CRP, IL-6, and IL-18 are increased in patients with OSA. Carotid plaque formation is associated with minimum nocturnal oxygen saturation.

A prospective study of 120 elderly patients (aged 79 ± 10 years) with acute stroke found a high incidence

of SDB within 24 hours of the onset of neurological symptoms. A history of snoring was found in 26% of patients and a history of witnessed apneas in 4%. In another study, 63 of 151 consecutive patients referred to a geriatric stroke rehabilitation unit 2–4 weeks after a stroke were found to have an AHI >15 [43]. These 63 patients (mean age 78 years) were randomized to either CPAP treatment for 4 weeks or to a control group without treatment. The treatment group had a significant improvement in depressive symptoms compared to controls. Obstructive sleep apnea has also been shown to be associated with higher mortality in patients with stroke, and poor functional outcomes in stroke survivors. However, consistent data from large epidemiological and prospective studies will be needed to confirm the association between stroke and OSA and to assess the effect of OSA on stroke outcomes. The association between sleep and stroke is discussed in detail elsewhere in this book.

Sleep disordered breathing and pulmonary hypertension

While some studies have suggested a concordance between OSA and pulmonary hypertension (PH), clear and convincing evidence of an association between these conditions is still lacking. Several studies suggesting such concordance were either small, methodologically flawed, lacked adjustment for confounders, or used a lower pulmonary artery pressure cutoff for defining PH than the currently recommended criteria [44]. The presence of PH in these studies has correlated with body mass index and low daytime arterial oxygen saturation rather than the severity of sleep apnea. Hence, it has been suggested that PH in OSA may be related to concomitant risk factors such as pulmonary parenchymal disorders, left heart disease, or obesity rather than OSA itself [44]. In the absence of cogent evidence supporting OSA as an etiological factor for PH, routine evaluation for PH in OSA patients is not advisable [44]. Conversely, it is not expedient to perform routine polysomnographic evaluation for OSA in patients with PH. However, a patient with PH with symptoms suggestive of OSA should undergo polysomnography with adequate treatment of any sleep disordered breathing. The preliminary evidence suggesting an association between obesity hypoventilation syndrome and PH is compelling but needs to be further substantiated. Some studies have suggested an alleviation of pulmonary artery pressures with regular CPAP use in OSA patients with PH. It is unclear whether the putative association between PH and SDB is the same in the elderly in comparison to those who are younger.

Insomnia and other sleep disorders

Insomnia is common in the elderly, with women being twice as likely as men to report difficulty falling asleep (30% vs. 14%) [22]. The relation between insomnia and cardiovascular disorders has been less well examined than that between SDB and cardiovascular disorders, especially in the elderly. The lack of a consensus definition for insomnia has further complicated the task of assessing any associated co-morbidities.

A meta-analysis of studies evaluating insomnia and coronary events demonstrated a 50–200% increased risk of CAD in persons with sleep problems [45]. Of the 10 studies included in this analysis, one looked exclusively at adults 65 years of age and older in North Carolina, while other studies looked at middle-aged participants or all ages. The study looking at subjects 65 years or older found incidence density ratios for fatal and non-fatal first MI over 3 years to be 1.67, 1.16, and 1.50 for trouble falling asleep, trouble staying asleep, and trouble waking too early, respectively, after adjusting for covariates. The association was stronger in persons aged 65–74 years, with no predictable increase in risk in older participants. A cross-sectional study in 1506 older adults (55–84 years old) demonstrated a significant association between recent history of frequent insomnia and presence of heart disease [46]. A more recent cross-sectional study of 772 men and women aged 20 to 98 years old (at least 50 men and 50 women in each decade from 20 to +80) confirmed the high prevalence of cardiovascular disease in those with insomnia [47].

Another study of members of the Swedish Pensioners' Association aged 65 years or older found a strong correlation between cardiac symptoms and several sleep complaints [48]. For both genders, chest pains were reported by at least twice as many persons with a history of difficulty falling asleep or with waking early as those without these complaints. A large study of 11 863 participants in the Atherosclerosis Risk in Communities (ARIC) Study without cardiovascular disease at baseline assessed the relationship between sleep complaints and incidence of heart disease. The participants who had difficulties with falling asleep, waking up repeatedly during night, and

awakening tired and fatigued had a modest increase in the incidence of cardiovascular disease (OR 1.5, 1.1–2.0) over a 6-year follow-up period [49]. The risk of developing hypertension or IHD was higher in the older age group (65–69 years) than in the younger age groups. Another study of 5201 participants of the Cardiovascular Health Study aged 65 and older revealed an independent association between sleep disturbances and angina [22].

Conversely, insomnia is more frequently reported in patients with heart disease, hypertension, or CHF (18–44%) [47]. Fragmented sleep and tiredness have been reported as late as 1 year after percutaneous transluminal coronary angioplasty (PTCA), suggesting that sleep problems may emanate from the medical disorder, or associated medical or psychiatric co-morbidities.

While the optimum sleep duration is still not clear, many authorities suggest that sleeping 7–8.5 hours may be ideal for the restorative function. Short or long sleep durations have been associated with a higher mortality in all age groups. In an analysis of responses from 1.1 million men and women aged 30 to 102 years, self-reported sleep durations of less than 3.5 or 4.5 hours or more than 8.5 hours were associated with higher mortality [50]. Furthermore, participants who reported prescription sleeping pill use had significantly elevated mortality risk, even after controlling for sleep duration, insomnia, and other co-variates. Both short and long sleep duration have been variably associated with increases in cardiac biomarkers in middle-aged adults. However, clear evidence that shorter or longer than "optimal" sleep duration predisposes to adverse cardiovascular outcomes in the elderly is still lacking.

Daytime sleepiness is common in the elderly and increases with age in both men and women [22]. Women with congestive heart failure and hypertension report more daytime sleepiness, while in men, carotid artery disease is independently associated with daytime sleepiness [22]. One study of 4578 adult participants in the Cardiovascular Health Study aged 65 years and older demonstrated an association between use of medications for congestive heart failure and daytime sleepiness [51]. Daytime sleepiness is associated with cardiovascular morbidity and mortality in older adults, especially in women [4].

Frequent nightmares are also common in the elderly. One study found increased nightmares to be associated with an increase in self-reported irregular heart beats and spasmodic chest pain in 6103 elderly subjects (39.5% men) [52].

Although the available data suggest that insomnia symptoms may be causal in the pathogenesis of cardiovascular disease, it is also possible that they are merely epiphenomena of the cardiac afflictions. Nevertheless, sleep disruption has been shown to be associated with prothrombotic mediators, which may facilitate genesis of cardiovascular disease. Immune function is altered in patients with insomnia, with lower levels of CD3+, CD4+, and CD8+ cells and a reduction in natural killer cell activity, interleukin-2 production, and lymphocyte enumeration in insomniacs. Sleep complaints are also associated with hypothalamic–pituitary–adrenal (HPA) axis dysregulation, inflammation, and endothelial dysfunction, which can all contribute to the pathogenesis of the cardiovascular disorders. Conversely, diverse factors associated with cardiovascular disorders such as pain, anxiety, depression, and side effects of medications may lead to sleep disturbances. Large prospective studies looking at people with sleep disturbances and controlling for confounding factors such as sleep disordered breathing and other medical and psychiatric co-morbidities as well as diverse medications will be needed to understand the association between insomnia complaints and CAD, and determine the direction of causality, if any.

Conclusion

Sleep disorders are common in the elderly and may predispose to diverse cardiovascular consequences. There is persuasive evidence suggesting a role for OSA in the genesis and progression of cardiovascular disorders. The most compelling evidence is that for the association between OSA and hypertension. The role of CPAP therapy in alleviating cardiovascular sequelae in elderly patients has been inconsistent. Continuous positive airway pressure may have a role to play in elderly hypertensive patients with daytime sleepiness. Furthermore, cardiac function and vascular homeostasis may improve with CPAP use. Nevertheless, larger, rigorously designed studies need to be undertaken to better elucidate the cardiovascular sequelae of OSA and the effects of OSA therapy on ameliorating cardiovascular outcomes in the elderly. The role of other sleep disorders in causation, and their treatment in attenuation, of cardiovascular disorders in elderly patients also needs to be further examined.

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Part 3
Chapter
25

Sleep disorders in the elderly

Insomnia in the elderly

Megan E. Ruiter, Gregory S. Vander Wal, and Kenneth L. Lichstein

Sleep and aging

There are many health-related changes that occur in older adulthood that are associated with reduced quality of life. Among the most prominent are changes in sleep patterns. These changes are accompanied by a greater likelihood of poor sleep [1] and they become more significant with age [2]. Furthermore, advancing age is also associated with a significant increase in the occurrence and severity of insomnia [3]. This chapter will briefly address age-related changes in sleep and the nature, assessment, diagnosis, and epidemiology of older adults with insomnia (OAWI) from a behavioral sleep medicine perspective.

Through the use of electroencephalography, electro-oculogram, and electromyogram, five stages of sleep have been identified that serve different and specific functions during a typical night of sleep. An in-depth discussion of these stages is beyond the scope of this chapter. However, these stages will be mentioned as they pertain to changes that occur with aging.

The structure, duration, depth, and continuity of sleep changes with age. As we age, our sleep typically becomes shorter, lighter, and more disjointed. Older adults tend to spend less time in deep sleep (stages 3 and 4) and more time in stages 1 and 2, which results in overall lighter sleep [4]. This can increase the likelihood that environmental antagonists, such as light and noise, will interrupt sleep. Older adults also tend to have shorter average sleep durations compared to younger adults [5], although they typically do not report a decreased need for sleep [6]. Slight increases in the frequency of naps in older adults may indicate some compensatory sleep behavior for this loss of sleep duration [2, 7]. Although evidence suggests that daytime napping does not interfere with night-time sleep in the elderly [8], excessive napping has been linked to negative health correlates including excessive daytime sleepiness, pain, depressive symptoms, and higher mortality risk [9, 10].

The continuity of sleep also suffers as individuals age. Sleep in elderly people typically shifts between sleep stages more frequently and is interspersed with more arousals [4]. Combined with the decrease in deep sleep and resulting propensity for light sleep, these changes indicate a presentation of sleep that is more disjointed than the sleep of younger individuals. Changes also occur in the structure and resilience of the circadian rhythm. The 24-hour sleep–wake cycle becomes less entrained, resulting in blurred differentiation between the wake and sleep periods. This deterioration is associated with advanced sleep phase shifts in older adults, where the typical onset and termination of sleep are several hours earlier than desired [11, 12]. This deterioration of the circadian rhythm is also associated with a decreasing ability to adapt to transient changes in sleep patterns associated with travel, shift work, and sleep deprivation [4, 13].

As we continue to age, changes in sleep structure become more significant though reported sleep needs remain relatively stable [2]. Combined with the increase in the presence of health changes, increased physical and mental illness, and increased exposure to pharmacology, these factors contribute to a greater probability for sleep disturbance, particularly insomnia, in older adulthood. However, this does not mean that we are doomed to insomnia when we reach older adulthood. The aging process in itself is not solely responsible for the increase in insomnia incidence. It is the presence of the aforementioned factors that increases the risk of insomnia in older adults [14]. Evidence shows that although we are at a greater risk for insomnia as older adults, healthy older adults have the same prevalence of insomnia symptoms as younger adults [14]. Also, the severity of poor sleep in older adults is not significantly different from middle-aged adults [15]. Older adults without insomnia also show the same ability to return to sleep after awakening during the night as young adults, despite an increase in the number of awakenings they experience [16]. Our ability to sleep

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well is not hindered by old age or the changes in our sleep structure per se, but we are at a greater likelihood of encountering an event, situation, or other factor associated with the onset of insomnia that can hinder our ability to sleep well.

Some of the most common factors that contribute to the development of insomnia are circadian changes, mental and physical illness, and pharmacological, psychophysiological and negative conditioning. Older adults are at greater risk for experiencing circadian, health, and pharmacological intrusions that contribute to insomnia [4]. They are also at greater risk for medical and psychiatric co-morbidities [6]. However prevalent these risks are in older adulthood, evidence suggests that a significant number of cases of insomnia are free of medical and psychiatric factors, which suggests that older adults with insomnia also face the usual risk of psychophysiological and conditioning factors precipitating insomnia [17]. These psychophysiological and conditioning factors include physiological arousal (cognitive or physical), tension (overly sensitive to the environment, noise, light), psychological characteristics (anxious or depressed thoughts), lifestyle practices (inactivity; lack of social interaction), negative conditioning (by misusing the bedroom), and poor learned sleep habits (consuming caffeine, alcohol, or nicotine close to bedtime; deliberately spending time awake in bed)[4,18].

The nature and duration of insomnia does change with age [4]. The onset of insomnia in older adulthood is more associated with health factors, but the onset of insomnia in younger adulthood is associated more with psychosocial stressors [19]. Psychosocial and lifestyle choices can contribute to sleep disturbance in older adults to a greater extent than in younger adults. Lack of a regular daily schedule [20] and a satisfying social life [18] appear to contribute to the propensity to develop insomnia in older age. The overall message is, although sleep changes in structure as we age, the ability to sleep well is not affected by the aging process. What does affect our ability to sleep well is an increase in the chance of experiencing a sleep disturbing event and the potential decrease in ability to quickly cope with an event.

Epidemiology

Complaints of insomnia are categorized into difficulty falling asleep, difficulty maintaining sleep, unwanted early morning awakenings, and non-restorative sleep often with daytime consequences such as excessive daytime sleepiness and fatigue. The estimated global prevalence of these sleep complaints among older persons aged 65 or older falls between 30% and 60% [21, 22, 23, 24]. The prevalence of chronic insomnia variously defined among the elderly has been found to range from 12% to 40% [21, 25, 26, 27, 28, 29]. According to quantitative criteria the point prevalence for chronic, clinically significant insomnia is 15.9% [3]. A recent review of epidemiological studies of insomnia by Ohayon concluded that the prevalence of insomnia increases with advancing age [30]. Our own research group has adopted empirically derived, quantitative criteria for insomnia and applied it to an epidemiological survey we conducted designed to measure the sleep experience across the entire adult lifespan [3]. Overall, our data are in agreement with the conclusions of Ohayon's review. Specifically, the changes in prevalence across the adult lifespan indicate that until decades 70–79 and 80–89 insomnia prevalence remains approximately stable during middle age. Those later decades in life mark a two-fold increase in prevalence from the mean rate.

Further corroborating these findings are studies on the incidence rates of insomnia in the elderly. Morgan and Clarke found that incidence rates over a 4-year span ranged from 2.8% to 3.5% in the 65–79 age group [31]. Two other studies found even larger incidence rates. One study produced an incidence rate of 7.3% over the course of 1 year [29]. Another study found an incidence rate of 5% over the course of 3 years. Similar incidence rates between the sexes were found, with the exception of a higher incidence rate in men 85 years and older [32]. This study also indicated that the complete remission of insomnia occurred in 15% of the study sample. Most recently, Morgan examined the cumulative 4- to 8-year incidence rate of insomnia and found a 3.6% per year increase in persons 65 years and older [33]. Notably, a significant predictor of the incidence of insomnia was older age. Specifically, the probability of reporting the incidence of sleep complaints nearly doubled in those 75 and older. In contradiction to these studies, other researchers have found no association between age and the incidence of insomnia; however, the persistence of insomnia over a 1-year span was significantly associated with older age [34]. Therefore, the suggestion was made that the rate of new cases does not increase with age but remission rates may dwindle with age. In fact, they determined that each decade increase in age is coupled with a 1.1 elevated risk of persistent insomnia.

The spike in insomnia in the later years has been found to be more pronounced in women than in men [21, 23, 26, 29, 33, 35]. In our research group, our data indicates that insomnia presence climaxes at 41% in women between the ages of 80–89 while men peak at 23% [3]. In agreement with these findings, a meta-analysis of sex differences in insomnia found that although across all ages women are at greater risk of developing insomnia than men. However, the risk is much higher in elderly women than in younger women [36]. Whether these changes are sex-specific remains to be determined, although evidence suggests that menopause and other related hormonal changes such as estrogen deficiency [37] as women age may interact to increase the vulnerability of women to developing insomnia [38]. Alternatively, data suggest that perceptions of sleep quality may be influenced by gender in older cohorts because older men tend to have a strong relation between their subjective and objective sleep while the relation for older women is much weaker [39].

There has been some interest in whether certain types of insomnia are more common at different ages. A common maxim held by sleep researchers is that insomnia associated with difficulty initiating sleep is most prevalent in younger adults and difficulty maintaining sleep is most prevalent in older adults [4, 40]. In addition, early morning awakenings are purportedly on the rise in the latter years but are nevertheless less prevalent than maintenance insomnia [4]. These assumptions have not been substantially supported by the literature as yet and warrant further investigation. The type of insomnia tends to direct clinicians towards certain psychological and pharmacological treatments that specifically target each type of insomnia. Our research group found that there is a soft trend for type of insomnia to correlate with age as suggested above; but overall, all types of insomnia commonly occur in all age groups [3]. Similarly, Ohayon and his colleagues, in a survey of over 13 000 people between the ages of 15 and 100, reported that type of insomnia was not associated with age [35]. Further data suggest that sleep onset and maintenance insomnia types are equally prevalent in the elderly, but that there may be gender differences in the predominance of insomnia type in this age group [23]. Specifically, co-morbid sleep onset and maintenance insomnia was most common in women, and maintenance insomnia was most common in men.

It should be noted that there is some evidence indicating ethnic differences in the epidemiology of insomnia. However, the data on this matter have been contradictory; therefore more empirical data are needed. Epidemiological data on older Caucasian Americans suggest that they report more sleep complaints than African-Americans and that the sharp rise in insomnia prevalence in older adults is less likely to occur among African-Americans [41]. A spike in insomnia among middle-aged African-Americans has been observed [3], and this pattern has not been reported in Caucasian samples. Further analysis revealed that these differences could not be accounted for by any daytime functioning or reported health problems [42].

Diagnosis

There is general consensus among diagnostic systems (DSM-IV-TR, ICD-10, ICSD-II) on basic features that constitute an insomnia diagnosis, although there are distinctions in how subtypes of insomnia are grouped and labeled [4]. There are essentially three main components of an insomnia diagnosis: (1) complaint of a sleep difficulty with (2) an adequate opportunity to attain sufficient sleep, and (3) accompanied by daytime impairment complaint. The range of subjective daytime functioning impairment includes excessive sleepiness, fatigue, poor concentration, worries about inadequate sleep, negative affective changes, and impaired cognitive functioning [43] that generally affect social, occupational, or physical areas of functioning [44]. Factors that interfere with the opportunity to obtain sufficient sleep include other sleep disorders, substance use, shift work, or the presence of another psychiatric disorder [44].

None of the current classification systems include quantitative criteria for measuring clinically significant sleep disturbance. General recommendations for sleep disturbance criteria range from ≥20 to 31 minutes of sleep onset latency (SOL) or wake time after sleep onset (WASO), 3–4 nights a week, for 6 months or longer [45, 46]. It is important to consider a balance between severity of insomnia nights and frequency of insomnia nights [46]. For older adults, ≥31 minutes of SOL or WASO appears to be better at differentiating people with insomnia from normal sleepers. It is important to remember that these sleep criteria must also be accompanied by distress about sleep and an insomnia complaint.

When diagnosing insomnia in older adults, there are differential diagnoses that must be ruled out. First, it is important to make a distinction between insomnia and sleep changes due to the aging process. The

changes in sleep structure, depth, and continuity that are associated with aging do not necessarily lead to insomnia, but can be easily misinterpreted as insomnia [4]. It is essential that not only the changes in sleep are assessed, but also the impact these changes have on daytime and psychosocial functioning. Also, it is important to understand the role of distress in insomnia. The presence of a complaint about sleep is an integral part of the diagnosis process. Research on sleep in older adults has shown that many individuals have disordered sleep based on quantitative measures, but are not distressed about their sleep pattern [47]. Thus, it is important to understand that the presence of what appears to be poor sleep based on objective standards does not necessarily reflect insomnia if it is not accompanied by sleep dissatisfaction and daytime symptoms.

It is also important to rule out other common sleep disorders. Increases in sleep-related breathing disorders and reports of periodic limb movements are associated with advancing age [48]. Assessing symptoms of sleep-related movement disorders such as restless legs syndrome or periodic limb movements, and assessing related breathing disorders such as body mass index, neck size, snoring, and daytime sleepiness through a thorough clinical interview is a useful way to gain an indication for the influence of either of these disorders in an individual's sleep complaint [49].

It is important to consider all these factors when making a diagnosis of insomnia, whether in older adults or the rest of the population. The increased likelihood of experiencing one or more of these factors and the natural changes associated with the onset of insomnia and the natural changes in sleep structure in older adulthood amplifies the importance of a comprehensive assessment of insomnia that addresses sleep and daytime functioning and includes a complete history and clinical interview.

Assessment

Assessment of OAWI in its most basic form is similar to assessment procedures with adults with insomnia. The necessary but not sufficient conditions to receive a diagnosis of insomnia are sleep complaints and subjective estimates of poor sleep quality. Therefore, subjective measures such as sleep diaries and retrospective questionnaires are the gold standard to assess for insomnia as opposed to such objective measures as polysomnography (PSG) and actigraphy. In fact, actigraphy has been labeled as a measure of poor clinical utility in assessing insomnia [50] for reasons such as it underestimates total wake time and sleep-onset latency and overestimates total sleep time and sleep efficiency in older adults [51]. However, the adequacy of actigraphy is instrument and algorithm specific. Our study demonstrated reasonable accuracy that was not age dependent [52]. In addition, if information indicates that activity levels may be affecting sleep, then actigraphy is the recommended measure for rest-activity patterns [49].

Despite similarities in the assessment among all adults, older adults create a much more complicated picture. The contributing factors, that were mentioned earlier, are often multiple and interacting, and the probability that current sleep disturbance persists from younger years increases. As a result, clinicians/physicians should keep the following principles in mind when faced with the challenge of assessing OAWI: (1) separate treatable causes of insomnia complaints from normal aging-related changes in sleep, (2) identify the most appropriate contributing factors for psychological and/or pharmacological intervention, and (3) take a careful sleep history [4]. Often, especially in medical practice, there is inadequate assessment and documentation [53], which highlights the importance of integrating these principles.

A sleep history is the first step to establishing insomnia in older adults. Kamel and Gammack suggest that a comprehensive sleep history confirms that the patient has a complaint of insomnia, and investigates the patient's sleep/wakefulness patterns [54]. The investigation should include the definition of the current primary sleep disturbance including its onset, duration, and severity. Subjective, behavioral, and physiological methods may all be necessary to obtain a complete profile of the sleep disruption [49]. For example, a recommended subjective measure is 1- to 2-week sleep diaries and global insomnia symptom questionnaires. An interview with a bed partner and the use of a wrist actigraph may reveal the behaviors that indicate or contribute to the presence of insomnia. In addition a family history of sleep disorders and a lifetime history of the patient's sleep may shed some light on what occurred during previous episodes of bad sleep, what was tried to relieve it, and if and how it was resolved. Assessment with older adults should also consist of a general medical and medication history in addition to physical and psychiatric evaluations. This

will help to identify possible medication effects and interactions as well as medical and psychiatric conditions known to interfere with sleep. Lastly, although the use of PSG as a physiological measure of transient or chronic insomnia is generally not indicated, its use is more often recommended with older adults because covert sleep-related physiological factors, such as sleep apnea and periodic limb movements, increase in prevalence with age [55]. Our study on occult sleep apnea in insomnia discovered that OAWI have a 29–43% rate of undiagnosed sleep apnea, which further highlights the need to follow this recommendation [56].

Several other assessment procedures are indicated by Fichten and colleagues to guide treatment decisions and to more accurately identify the sleep problem [57]. These procedures include the evaluation of psychologically laden characteristics of sleep such as distress and self-efficacy beliefs about sleep. It is also important to gauge daytime psychological and behavioral adjustment to the sleep problem in terms of anxiety, neuroticism, depression, sleepiness, and fatigue. Assessment of personality factors and coping styles may also illuminate factors that may contribute to the sleep problem [48]. Finally, identification of negative cognitive activity and behaviors that are not conducive to sleep either during the daytime or during nocturnal wake times allows the construction of a comprehensive profile of the older patient's insomnia experience and directs how to best treat the problem [57].

Clinical features of late-life insomnia

There are several contributing factors that conspire and create the experience of insomnia in the elderly. Broadly, they can be grouped into mental and physical health, environmental/situational, behavioral, and personality factors. Clinical features found most often to affect OAWI in each one of these groupings are discussed below.

The utility of insomnia as an indicator of poor mental health has long been established as well as its reciprocal contribution [58].The elderly with chronic insomnia in particular have a greater risk of developing depression especially for women and those experiencing difficulty maintaining sleep [59]. However, it is suggested that poor mental health may not be as strong a contributing factor in OAWI compared to the multitude of other contributing factors that may not occur as often in younger age groups [4]. Nonetheless depression and anxiety are still highly prevalent and frequently contribute to insomnia in the elderly [4, 60]. Several events that frequently occur in older age such as retirement, bereavement, social isolation, co-morbid disease, and dementia tend to be risk factors for depression [60], which may affect OAWI more keenly. In fact, evidence shows that depression and physical health are independent predictors of insomnia in the elderly [4]. Studies show that physical illness may contribute a greater role in the manifestation of insomnia in older adults compared to younger samples [35, 61]. Common diseases that contribute to co-morbid insomnia, or the presence of insomnia co-morbid with other conditions [62], include nocturia, congestive heart disease, musculoskeletal disorders, arthritis, gastrointestinal illness, bronchitis, dementia, and diabetes [23, 60]. In addition physiological disorders such as sleep-related respiratory disturbance, neurological disorders such as Alzheimer's disease and Parkinson's disease, substance use disorders due to the prevalent practice of polypharmacy among the elderly [60], and circadian rhythm disorders contribute to late-life insomnia. Many sleep disorders that often co-occur with an insomnia complaint are also more common or have their initial onset in older age groups.

Situational factors that are generally found among OAWI are institutionalization, bereavement, retirement, and cultural influences. Institutions such as nursing homes have been found to directly affect sleep quality in its residents due partially to noise in these settings [4]. Bereavement often can be a trigger for chronic insomnia in the elderly especially in such cases as the death of a spouse. As mentioned above, a stressful life event such as this may put the older person at risk for depression, which may consequently contribute to the onset of insomnia. The effects of retirement like a decrease in daily scheduled events may influence sleep/wake patterns. Lastly, sociocultural factors may influence the sleep/wake patterns and sleep duration in the elderly by nation or region [18]. For example, several sociodemographic variables that may influence sleep/wake patterns, such as the emphasis on labor as a normative role the elderly participate in, are different among nations.

There has been considerable debate over the behavioral factors that may be frequently found in OAWI. The lifestyles of older adults have often been made the culprits of the onset and maintenance of insomnia. For instance, it has been suggested that older adults may become more sensitive to the effects of alcohol and caffeine and thus those who consume caffeine or

alcohol may be at risk for degradation in sleep quality [60]. In addition, excessive time spent in bed and excessive napping are frequently associated with OAWI [4]. However, as mentioned earlier there is conflicting data on napping on whether it is beneficial or detrimental to the sleep quality of elders. It is suggested that the duration of naps rather than the frequency may be harmful to nocturnal sleep [9].

There is also evidence that shows how several lifestyle factors fail to differentiate OAWI from age-matched normal sleepers. These lifestyle factors include usual bedtimes, arising times, napping frequency, amount of time spent in bed, alcohol or coffee consumption, and diversity of activities [57]. Reports in the literature do seem to be in agreement that a low level of physical activity is a frequent feature and contributor to insomnia in older adults. Specifically, low physical activity levels are a significant risk factor for acute and chronic insomnia but high levels of physical activity, independent of those activities associated with social involvement, may serve as a buffer against these insomnias in old age [33].

There is a stereotypical profile of the personality features found often in OAWI. Elevated levels of neuroticism and anxiety have been found in all cases of poor sleepers. These personality traits are assumed to endure into older age; therefore, it is widely considered that they may be risk factors for insomnia in the elderly if the onset of insomnia had not already occurred earlier in life [4]. Furthermore, OAWI tend to worry, employ behaviors not conducive to sleep, toss and turn in bed, have subclinical levels of depression, have increased mental and physical tension, have negative thoughts during the night, and have higher cortical arousal [57, 63]. Recent data has implied that these personality traits in the elderly have an influence on the perception of sleep that often does not reflect their sleep when measured by PSG or actigraphy [64].

Daytime functioning in insomnia

OAWI often cite reduced daytime functioning and quality of life as frequent consequences of sleep disturbance. Poor daytime functioning factors, such as those mentioned earlier, may also reciprocally contribute to sleep complaints suggesting a cyclical relationship [65]. The operationalization of these perceived daytime consequences has met little success (for a review see Riedel and Lichstein [43]). Investigations often have found that, despite complaints of daytime impairment among OAWI, there is no significant difference between people with insomnia and those without on objective measures (e.g. reaction time, the Multiple Sleep Latency Test [MSLT], digit symbol substitution, card sorting, logical reasoning). However, older adults often experience significantly worse performance lapses and decreased ability to recognize situations where their performance ability is impaired [66]. Lastly, subjective measures reliably separate OAWI from healthy controls (e.g. Minnesota Multiphasic Personality Inventory [MMPI] depression and anxiety scales, Profile of Mood States, Beck Depression Inventory, State-Trait Anxiety Inventory, Dysfunctional Beliefs and Attitudes about Sleep Scale, Insomnia Impairment Scale, fatigue ratings and some subjective daytime sleepiness scales).

In contradiction to previous research, new findings imply that more challenging and cognitively demanding objective tasks such as task-switching separate OAWI from age-matched controls [67]. It appears that OAWI may be able to utilize compensatory mechanisms for easier tasks that make them indistinguishable from healthy older adults, but these mechanisms fail to do their job when the cognitive tasks are increased in difficulty. Also, factors that interfere with the retrieval of compensatory mechanisms may differentiate the groups on less cognitively demanding tasks such as response speed. In one study, proximal skin warming impeded speed on a reaction time task in OAWI compared to older adults without sleep complaints [68]. While age-related response speed slowing is often found with aging it appears that pronounced age-related cognitive slowing may actually be a product of chronic age-related sleep problems. Further evidence suggests that chronic insomnia in the elderly even detrimentally affects their visual-perceptual processing above and beyond normal aging processes [69].

Conclusions

The incidence, chronicity, and complaints of insomnia increase with age and are associated with numerous daytime impairments, decreased quality of life, and cognitive decline above and beyond normal aging processes. As one moves from middle age to the later years of life, the aging process creates changes in sleep architecture and continuity that increase the vulnerability to developing chronic insomnia. However, it is well established that these aging processes do not directly and inevitably cause insomnia but rather several age-correlated risk factors may have greater

immediacy in promoting insomnia. These age-correlated risk factors, normal changes in sleep structure, increased prevalence of various sleep disorders, and elevated levels of neuroticism increase the risk of acute insomnia becoming persistent and decrease the ability to adapt to normal transient occurrences of insomnia. When presented with OAWI it is important to differentiate insomnia from normal sleep changes due to aging, identify the relevant contributing risk factors, and take a thorough sleep history to determine the most appropriate psychological and/or pharmacological interventions for that individual. Research indicates that some crucial interventions that buffer against chronic insomnia may help the older adult to adopt a regular daily schedule, a healthier lifestyle and sleep behaviors, and increase the quality of social interactions and physical activity.

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Part 3
Chapter
26

Sleep disorders in the elderly

Sleep in nursing home residents

Jennifer L. Martin

A description of nursing home residents

Worldwide, the population of older adults is increasing, a phenomenon that has led to the increasing use of institutional facilities such as nursing homes to serve the long-term care needs of these individuals. As a result of the increasing use of nursing homes, understanding and managing the care needs of this subgroup of the geriatric population has become increasingly important. Residents of nursing homes are in need of care that cannot be provided in the home setting, and both functional and cognitive limitations are common. While worldwide data are not readily available, there were over 18 000 nursing homes with approximately 1.6 million residents in the United States in 1999. At that time, the average length of stay was about 2.4 years [1]. Although more recent national surveys are not available, one can comfortably assume the number of nursing home residents in the USA alone may now exceed 2 million residents. In the USA, the typical nursing home resident is White (88%), widowed (63%), female (75%), and over age 75 (86%). Residents of nursing homes generally do not return home. Only 29% of residents are discharged because they recover or are sufficiently stabilized to return home; however, most either die in the facility (27%) or are sent to acute care hospitals (28%) due to deteriorating health or acute medical emergency [2].

A description of sleep among nursing home residents

Sleep patterns of nursing home residents are extremely fragmented. This is manifested not only as disrupted night-time sleep, but also by frequent daytime sleeping. In fact, a nursing home visitor can readily see evidence of disrupted sleep patterns by noting the proportion of residents in bed during mealtimes or asleep during social activities in the nursing home. A large literature documents the sleep difficulties that occur in nursing home residents, and four studies have examined sleep disturbance among representative samples of nursing home residents [3, 4, 5, 6]. The largest study (N > 34 000), conducted by Avidan and colleagues [4], used data from the Minimum Data Set 2.0 (MDS 2.0), which is completed by facility personnel for all residents of nursing homes in the USA on a twice-yearly basis. In that study, 6.3% of nursing home residents were indicated to have "insomnia" on the MDS. One major caveat of that study was the use of the MDS, which was not designed to detect the prevalence of true insomnia, and the fact that the insomnia item with the MDS is included as a symptom of depression rather than as a distinct disorder [7]. A second study of over 2000 residents used interviews with nursing staff and found that 6.2% of residents were identified as having insomnia, with 17% of residents displaying at least one insomnia symptom. Two smaller studies (N = 26 and N = 492) [3, 5] used direct observation of patients by research staff [5] and wrist actigraphy [3, 5] to assess sleep. These studies found substantially higher rates of objectively disturbed sleep. Martin *et al.* [5] reported that 69% of patients were sleeping excessively during the day (defined as "asleep" during >15% of observations from 09:00 to 17:00), and of those individuals, 72% also slept less than 80% of the night (based on wrist actigraphy from 22:00 to 06:00). In a smaller study by Fetveit and Bjorvatn [3], the average characteristics of sleep showed residents took an average of 1 hour to fall asleep, were awake for over 2 hours during the night, spent over 13 hours in bed at night, and napped on 87% of the days recorded. Taken together, these studies show that nursing home residents commonly suffer from sleep disturbance, a phenomenon that is not actively investigated or dealt with in most nursing homes.

Several additional studies have shown that sleep disturbance in nursing homes is a 24-hour condition [9, 10]. Residents are often asleep intermittently at all hours of the day and night, and the typical nursing

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home resident shows a pattern of wakefulness that is frequently interrupted by brief periods of sleep. This is different from what has been seen in community-dwelling older adults, who may typically take a regular nap during the day at a specific time. In the nursing home, non-restorative daytime dozing is typically accompanied by night-time sleep that is interrupted by frequent awakenings. It is impossible to determine which is causal and which is symptomatic and likely it is a circular pattern of night-time wakefulness contributing to daytime sleeping and vice versa. Over the long term, however, the pattern of daytime sleepiness and napping most certainly perpetuates abnormal sleep patterns. On average, residents are rarely asleep or awake for a continuous hour during the day or night [9], and in extreme cases, the sleep of nursing home residents can be distributed evenly across the 24-hour day.

Consequences of poor sleep in the nursing home

Poor sleep represents more than a mild annoyance for nursing home residents. A vast and growing literature across age groups shows that disrupted sleep is related to negative health outcomes, disease, and mortality risk. Recent findings suggest that short periods of sleep at night, poor sleep efficiency (percent of the time spent in bed actually asleep), and increased napping during the day are all associated with an increased risk of falls [10], an increased risk of a reduced lifespan [11, 12] as well as other negative outcomes in the nursing home setting [4, 13]. Falls are a serious concern for the elderly, and the Centers for Disease Control and Prevention (CDC) in the USA found that, in 2003, a total of 13 700 persons over age 65 died from falls, and 1.8 million were treated in emergency rooms for non-fatal fall-related injuries [14]. Clearly, the relationship between sleep disturbance and falls in nursing homes cannot be taken lightly.

Factors contributing to poor sleep in the nursing home

Although the specific causes of sleep pattern disruption vary from person to person, there are several common causes of sleep difficulties in the nursing home setting. These include medical conditions, psychiatric disorders, medications/polypharmacy, circadian rhythm disruption, and primary sleep disorders. Environmental factors (e.g. noise and light during the night, low daytime indoor illumination, little time spent outdoors) and behavioral factors (e.g. physical inactivity, extended time spent in bed) also appear to contribute to the disruption of sleep/wake patterns among residents of nursing home facilities.

Medications, medical illnesses, and psychiatric disorders

Nursing home residents often suffer from multiple medical and psychiatric co-morbidities and are often in poor physical health. Examples of medical conditions and symptoms that may contribute to sleep difficulty for nursing home residents include pain (e.g. from arthritis), paresthesias, night-time cough, dyspnea (from cardiac or pulmonary illness), gastroesophageal reflux, and incontinence/frequent night-time urination; however, this list is far from exhaustive. While many of these are chronic conditions that cannot be treated directly, many require ongoing symptom management. In such cases, treatment should consider daytime alertness and functioning and maintenance or improvement in night-time sleep quality as important correlates of effective treatment.

Sleep abnormalities are directly associated with neurological illnesses (e.g. Alzheimer's disease, Parkinson's disease) as well, and residents of nursing home facilities are often in the late stages of neurological disease. Patients suffering from dementia have more sleep disruption (including lower sleep efficiency, more light sleep, less deep sleep, and perhaps less REM sleep) compared to older people who do not suffer from dementia. Some symptoms of dementia, such as irritability, poor concentration and memory, slower reaction time, and decreased overall cognitive performance may be exacerbated by sleep problems, particularly by daytime sleepiness. Sleep and circadian rhythm disruption is associated with dementia symptoms among older people in the nursing home and community settings [15, 16, 17]. "Sundowning," the term used to describe a worsening of confusion, agitation, and behavior problems in the evening or night in people with dementia, may have an underlying neurological basis and is associated with circadian rhythm disruption [18]. Sleep abnormalities such as excessive daytime sleepiness and parasomnias (e.g. REM sleep behavior disorder), which are associated with Parkinson's disease, may be related to the pathology of the disorder and/or to its pharmacological treatment. Problems may be even more common among nursing home residents with advanced disease [19].

Depression is also common among nursing home residents and accounts for a large proportion of psychiatric consultations in the nursing home setting [20]. Depression is associated with poor quality of life [21] and increased use of benzodiazepines for sleep [22] in nursing home settings. Sleep disruption is a common symptom of depression, and it is often difficult to discern whether a true sleep disorder exists independent of depression in people suffering from both conditions. While studies have not been conducted in the nursing home, research in outpatient settings suggests that treating sleep disturbance can have beneficial effects on depression [23]. Future research is needed to determine whether treating sleep problems in depressed nursing home residents might have similar beneficial effects.

Nearly all nursing home residents take multiple medications to manage their medical and psychiatric difficulties. Nursing home residents typically take 5–8 different medications each day and some take more than 10 medications daily [9, 18]. Owing to the absolute number of medications used, one or more of these medications is likely to impact night-time sleep, daytime alertness, or both. Some medications can be particularly problematic when taken near bedtime; for example, diuretics can increase nocturnal urination and stimulating agents (e.g. sympathomimetics, bronchodilators) can directly disrupt sleep at night. The use of sedating medications during the daytime (e.g. antihistamines, anticholinergics, sedating antidepressants, sedating antipsychotics) can contribute to daytime drowsiness, leading to daytime sleeping and further disrupting night-time sleep. Some medications used in the treatment of depression, Parkinson's disease, and hypertension can impair sleep or cause nightmares. While medications may be necessary, changing the timing of administration of a medication can ameliorate sleep difficulties in some cases, particularly if sleep difficulties started or were exacerbated when the medication was first administered.

Circadian rhythms in the nursing home

Circadian rhythm changes contribute to sleep problems in nursing home residents. Among older adults in general, circadian rhythms may be blunted in amplitude and can be shifted to abnormal times. Circadian rhythm changes are also seen among individuals with dementia, although the type of disruption depends upon the type of dementia. In one study, nursing home residents had less stable circadian rhythms of activity compared to older people living at home, regardless of cognitive status [24]. Other studies have found a relationship between circadian rhythm disturbance and degree of dementia in the nursing home setting [25] and circadian activity rhythm abnormalities have been associated with shorter survival [17].

The often-cited age-related advance (i.e. shift to an earlier time) of circadian rhythms can be exacerbated by environmental factors in the nursing home. Exposure to bright light, the strongest synchronizer and stabilizer of circadian rhythms, is limited in the nursing home environment and nursing home residents seldom go outdoors [5]. Studies show that nursing home residents are exposed to only a few minutes of bright light per day. This is both insufficient for entrainment of circadian rhythms, and is less than the light exposure levels of community-dwelling older people [26]. Since light exposure is the strongest known *zeitgeber* (time cue) in humans, this lack of daytime light may contribute to circadian dysregulation and subsequent sleep irregularities. A second factor that can contribute to circadian rhythm disturbance is physical inactivity. One study found that residents of nursing homes with lower staffing levels were in bed on 40% of daytime observations while those of homes with higher staffing levels were in bed on 26% of daytime observations [27]. In our own work, we found that residents were in their own rooms on 29% of daytime observations and were in bed 27% of daytime observations [5]. These studies suggest that, in addition to long periods of in-bed time at night (13 hours, on average) [3], residents spend 2 additional hours in bed during the day. While physical limitations and fragile health status may contribute to some increase in time in bed, this can have deleterious effects on sleep and overall health. A typical resident might spend only 9 hours per day out of bed. While physical activity is a less potent factor in terms of circadian entrainment, lack of physical activity likely contributes to circadian rhythm disturbance in the nursing home setting.

One hypothesis is that disruption of circadian rhythms underlies the chronicity of fragmentation of sleep and wakefulness. This is because circadian rhythms exert a strong influence on the timing of sleep, and weak circadian rhythms or rhythms that are shifted to inappropriate times are likely to cause long-standing sleep problems. Circadian rhythm disturbances are best treated with timed exposure to bright light, and perhaps by increased daytime physical

activity. Several studies have found that exposure to bright light strengthens and stabilizes circadian rhythms in the nursing home [28, 29, 30]; however, the optimal timing of bright light exposure among nursing home residents remains somewhat unclear.

Primary sleep disorders in the nursing home

To our knowledge, no large-scale epidemiological studies have been conducted to examine the prevalence of primary sleep disorders in nursing homes. One could assume, however, that sleep disorders that increase in prevalence with advancing age (e.g. sleep disordered breathing [SDB], restless legs syndrome [RLS], periodic limb movement disorder [PLMD], REM sleep behavior disorder [RBD]) are at least as common among patients in nursing homes as in older adults in community settings. In addition, some sleep disorders are more common among individuals with certain dementing illnesses than among older adults without dementia (see Table 26.1). The absence of true prevalence information in the nursing home setting is, in part, due to the difficulty in conducting polysomnographic sleep recordings with nursing home residents, especially among individuals with dementia or extreme frailty; nonetheless, studies with non-representative samples and/or modified recording equipment suggest that SDB is a common problem.

Sleep disordered breathing is a condition in which the airway collapses during sleep or central nervous system signaling is impaired, leading to reduced airflow during respiration. These respiratory events can involve a complete cessation of airflow (apnea) or a partial reduction in airflow (hypopnea). Events lasting at least 10 seconds are considered clinically important, and when more than 15 events occur per hour of sleep, treatment is warranted. Sleep disordered breathing can lead to decreased oxygen saturation and interruption of night-time sleep. Both of these can contribute to negative consequences such as increased risk for cardio- and cerebrovascular disease, cognitive difficulties, and symptoms of depression. Depending upon the precise criteria and study design used, about half of nursing home residents have at least mild SDB [31, 32]. In nursing homes, SDB has been associated with cognitive impairment, agitated behaviors, and increased mortality risk [33, 34]. The standard treatment for SDB is continuous positive airway pressure (CPAP). While this treatment is not curative, it is highly effective in reducing the number of respiratory events. CPAP involves wearing a mask over the nose, which is connected via a hose to a machine that generates positive air pressure. The positive air pressure acts as a splint to hold the airway open. While CPAP has not been evaluated in the nursing home setting, recent findings suggest that Alzheimer's disease patients living at home with a caregiver have the same level of compliance with CPAP as general sleep disorders clinic patients [35]. This suggests CPAP should still be considered the treatment of choice among individuals in the nursing home who suffer from SDB, and residing in a nursing home should not necessarily preclude treatment of SDB [32].

Table 26.1. Sleep disorders that are more common in specific dementing illnesses

Sleep disorder	Dementia type
Sleep disordered breathing	Alzheimer's disease
	Parkinson's disease with dementia
	Vascular dementia
Restless legs syndrome	Dementia with Lewy bodies
	Parkinson's disease with dementia
REM behavior disorder	Dementia with Lewy bodies
	Parkinson's disease with dementia
Periodic limb movement disorder	Dementia with Lewy bodies
	Parkinson's disease with dementia
Circadian rhythm sleep disorders	Alzheimer's disease (delayed phase)
	Fronto-temporal dementia (advanced phase)
	Vascular dementia (various types)

Restless legs syndrome is a disorder in which, while at rest, an individual experiences uncomfortable sensations in the legs, and the discomfort is relieved with movement. RLS is important to consider in terms of sleep because symptoms often grow worse late in the day and contribute to difficulties falling asleep. RLS increases in prevalence with age, and individuals with RLS often report that their symptoms grow worse with age. This condition has not been studied in nursing homes; however, it may be a possible cause of motor restlessness and wandering among residents with RLS and dementia. Research in this area is needed, as RLS may represent a reversible cause of pacing and wandering at night. Periodic limb movement disorder is a related condition in which the legs jerk or kick during sleep. These movements can lead to awakenings from sleep and as a result, to high levels of daytime sleepiness. Medications, typically dopaminergic agents, are used to treat RLS and PLMD. There are two FDA-approved agents for the treatment of RLS: ropinerole (Requip) and pramipexole (Mirapex). These agents have not been studied in nursing homes and a careful consideration of the risks/benefits of these treatments would be required before initiating therapy.

REM sleep behavior disorder (RBD) is a condition in which the central nervous system mechanisms that control muscle paralysis during REM sleep fail, and the sleeper "acts out" his or her dreams. In the nursing home setting, this condition has not been studied; however, the prevalence of RBD is greatest in men over the age of 70 and among older persons with certain dementing illnesses (see Table 26.1). The main concern associated with RBD is the safety of the individual with the disorder. RBD sufferers can fall out of bed or engage in dangerous behavior while acting out dream-related behaviors during sleep. Clonazepam (Klonopin) is the treatment of choice for RBD, and it is effective in about 90% of cases. Treatment also involves securing the sleep environment to insure safety.

To date, no studies have systematically examined treatment of SDB, RLS, PLMD or RBD in nursing home residents. The safety and efficacy of these treatments for nursing home residents specifically is therefore unknown. In general, the treatment of nursing home residents with primary sleep disorders should closely parallel the treatment of frail older adults in the community. The risk/benefit ratio of each treatment should be considered, including potential drug interactions. The focus of treatment should be on improving the individual's functional status, cognition, and quality of life.

The night-time nursing home environment

During the night-time hours, nursing homes are generally more similar to in-patient hospital settings than home sleep environments. Residents typically share rooms with one or more roommates, and frequent noise and light interruptions (occurring several times per hour) are a direct cause of awakenings from sleep [36]. Much of the noise produced in the facility is caused by staff, often while they provide care for incontinence and other personal needs of residents at night [36, 37]. In addition to noise, night-time exposure to room-level light has the potential to suppress endogenous melatonin levels, disrupt sleep, and shift circadian rhythms [38]. Lights are commonly left on at night in patient rooms and in hallways, often by well-intended staff members who provide night-time care to patients. One key aspect of improving nursing home residents' sleep is to reduce night-time noise and light in patients' rooms.

Medications for the treatment of sleep problems in the nursing home

As a result of the Omnibus Budget Reconciliation Act (OBRA) of 1987 (which became effective in 1991), the use of regulated psychoactive medications in nursing homes in the USA must be documented in the medical record as necessary to treat a specific condition. Documentation relating to daily dose limits, requirements for monitoring treatment and adverse reactions, and attempts at dose reductions and discontinuation whenever possible are also required. The guidelines provide options for using psychoactive medications outside of the stated limits when clearly clinically indicated. Since the OBRA guidelines were implemented, research has shown substantial decreases in the use of antipsychotics, no change in the use of sedative-hypnotics and anxiolytics, and an increase in the use of antidepressants [39].

While many agents are approved for the treatment of insomnia, a number of additional medications are commonly used "off label" to manage sleep problems. In the USA, trazodone, a sedating antidepressant, is the most commonly used agent for treating sleep complaints [40]. The National Institutes of Health (NIH) convened a State-of-the-Science Conference

on Insomnia in 2005. The Panel concluded that the newer, shorter-acting non-benzodiazepine hypnotics were more effective and safer than older, longer-acting benzodiazepines and clearly stated that all antidepressants have potentially significant adverse effects, raising concerns about the risk–benefit ratio when these medications are used to treat sleep problems in the absence of depression. In addition, barbiturates and antipsychotics have significant risks, and thus their use in the treatment of chronic insomnia was not recommended. Finally, with regard to antihistamines (H1 receptor antagonists), there is no systematic evidence concerning their efficacy and there are significant concerns about their risks when used to treat sleep disturbances [35]. The conclusions of the NIH panel were based primarily on studies conducted with relatively healthy younger and older adults, not with dementia patients or with nursing home residents. There are published reports on the efficacy and safety of newer, shorter-acting non-benzodiazepines in older adults in the community [41, 42], and research is still needed in the nursing home setting to establish the safety and efficacy of these newer medications prior to advocating their widespread use.

When considering pharmacological therapy for sleep problems in the nursing home, it is critical to consider the possibility that these medications can increase risk of some adverse outcomes, particularly falls [43, 44, 45]. It remains unclear how much of this increased risk may be accounted for by the underlying sleep problems precipitating the hypnotic use. Based on a study using MDS data, an indication of insomnia (but not an indication of hypnotic use) was independently associated with increased fall risk after controlling for many (but not all) fall risk factors documented on the MDS [4]. These findings must be interpreted with caution since there are no data to support the accuracy of the insomnia or hypnotic use items on the MDS and there is evidence that documentation of falls using this method is substandard [7]. Research is needed in the nursing home setting to examine the relationship between untreated insomnia and risk of falls relative to the potential risks of pharmacological treatment.

A second critical consideration is that, given the large number of medications nursing home residents already use, there is a potential for drug interactions and/or altered drug metabolism when a hypnotic agent is added to the medication list. Finally, use of pharmacological agents for sleep problems should not be viewed as a substitute for addressing other underlying causes of sleep disturbance such as sleep apnea, night-time noise, inadequate control of pain, or circadian rhythm disturbances.

Non-pharmacological treatments of sleep problems in nursing homes

Investigators have studied the effectiveness of non-pharmacological interventions in the nursing home setting, and have found some success. Multiple studies have tested the effects of timed exposure to bright artificial light as a means of improving circadian rhythms and sleep/wake patterns in the nursing home. Bright light exposure impacts circadian rhythms and can also increase alertness levels during and immediately after exposure. In randomized-controlled trials, nursing home residents exposed to bright light showed improved sleep relative to participants who received placebo interventions [29, 30, 46, 47]. Researchers have also examined the effectiveness of supplemental melatonin (a hormone, typically secreted at night, that is closely linked to sleep), but results are mixed and optimal administration timing, dose, and preparation (acute vs. sustained release) are not clear. A few studies have attempted to increase daytime activity levels, and results are mixed. Some studies show improvements in sleep, while others show minimal or no sleep changes [48]. Studies have also attempted to reduce night-time noise and light in resident rooms. These studies have shown that it is extremely difficult to change the nursing home environment, and despite considerable efforts by researchers, the environment remained quite noisy at night [46, 48, 49]. It therefore remains unclear whether reduced noise would lead to improved sleep.

An alternative approach is to use multi-component interventions to address both internal physiological causes of sleep disturbance and external environmental factors. One such study tested a short-term (5-day) intervention combining daytime light exposure and physical activity, a structured and regularly timed bedtime routine, reduced time in bed during the day, and provision of night-time nursing care in a manner that minimized sleep disruption [46]. This intervention successfully reduced daytime sleeping, and increased participation in social and physical activity compared to usual care; however, night-time noise and light were not significantly reduced, and the intervention had a minimal effect on night-time sleep. There were also improvements in rest–activity rhythms with this

intervention [29]. Perhaps interventions left in place for long periods of time (i.e. weeks or months) might lead to greater improvements in sleep. Table 26.2 summarizes key components of addressing sleep problems in nursing home residents.

One final area for intervention, largely overlooked by the research community, is working at the facility level to change staff training, policies, and care-giving practices that impact resident sleep. In our own qualitative work, nightshift care-giving staff were aware of the difficulties created by residents having disrupted sleep; however, they felt a key aspect of their work was to check on residents regularly (often with lights on), and to provide night-time care. A second issue is the reduction of overall time in bed from the current average of around 15 hours per 24-hour day. This will likely be a necessary step in reducing sleep fragmentation. The addition of sleep-promoting practices and the removal of unnecessary sleep-disruptive activities may lead to meaningful improvements for all residents in a facility. Real change will require administrators and other staff to recognize that sleep is important and encouraging better sleep would benefit both residents and staff over the long term.

Summary and conclusions

Night-time sleep disruption and daytime sleepiness are characteristic of nursing home residents. In nursing homes, sleep disturbance is caused by a multitude of factors, including medical and psychiatric illness, medications, circadian rhythm abnormalities, SDB and other primary sleep disorders, environmental factors, and lifestyle habits including extended time in bed. Sleep disturbance is associated with negative outcomes among nursing home residents. While data to support the use of pharmacotherapy for sleep in the nursing home are limited, there is some suggestion that disturbed sleep improves with non-pharmacological treatments; however, these treatments have not been adapted for implementation into routine care. Further research on the implementation of non-pharmacological treatments within the nursing home setting is needed. Research is needed to determine whether treating SDB and other primary sleep disorders is feasible and results in functional or quality-of-life improvements among nursing home residents. Additional work is also needed to understand the facility-level factors that might lead to systemic changes in how sleep is viewed and sleep problems are addressed in nursing home settings.

Table 26.2. Key aspects of addressing sleep problems in the nursing home

Target symptom/problem	Strategy
Night-time sleep disruption	• Evaluate night-time sleep: consider primary sleep disorders and the night-time environment as likely causes of sleep disruption
	• Reduce time in bed at night by delaying bedtime in the evening
	• Take steps to reduce sources of night-time noise and light in the resident's room. Close door to resident's room if safety permits
	• Limit daytime sleeping to 1 hour nap in the early afternoon
	• Check for and (when possible) discontinue or adjust alerting/activating medications given late in the day
Excessive daytime sleeping	• Evaluate night-time sleep: consider primary sleep disorders and the night-time environment as likely causes of insufficient night-time sleep and resulting daytime sleepiness
	• Increase daytime exposure to bright light
	• Increase daytime physical activity
	• Check for and (when possible) discontinue or adjust sedating medications given during the day
Irregular sleep/wake patterns	• Reduce time in bed at night and adhere to a regular schedule for bedtime and morning rise time
	• Limit daytime in-bed time to 1 hour in the early afternoon
	• Increase daytime light exposure, physical activity, or both

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Part 3
Chapter
27

Sleep disorders in the elderly

Fatigue and sleepiness in the elderly: risk factors and management strategies

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Introduction

Daytime sleepiness and fatigue in the elderly are frequent complaints, but these are not necessarily an inevitable consequence of aging. At the same time, it appears that there is a common belief that increased sleepiness during the day, and also fatigue, tiredness, and lack of energy, are normal signs of an advanced age.

It is true to say, however, that older age comes with increased incidence of a variety of medical disorders that may cause daytime sleepiness and fatigue, and also with physiological changes that affect the quality and duration of overnight sleep, as well as the rhythmicity of sleep distribution. All of this may result in an increased need to sleep or rest during the day.

A number of studies have demonstrated that daytime sleepiness is rather related to poor health and not necessarily old age per se. A study by Asplund [1] showed a five-fold increase in the incidence of daytime sleepiness in people with poor health, compared to those with good health. Most common medical conditions associated with daytime sleepiness were cardiovascular disorders, diabetes, and musculoskeletal/painful disorders. In this study, close to a third of elderly males and a quarter of elderly females reported feeling sleepy during the day, and 30% and 15%, respectively, took daytime naps (in contrast to 9% of the general population who report daytime sleepiness) [2]. Conversely, excessive daytime sleepiness (EDS) is a predictor associated to a number of medical conditions, including stroke, congestive heart failure, myocardial infarct, depression, dementia, and global functioning [3, 4, 5]. These findings were based on studies that differed in methodology, and are disputed when it comes to the ultimate of outcomes – an overall increase in mortality [6]. This notwithstanding, there is enough evidence to prompt caution when it comes to daytime sleepiness and fatigue in an otherwise asymptomatic elderly patient. Sufficient evidence exists that EDS is often multifaceted and connected to various medical conditions, which, in turn, makes it worthwhile spending additional time and effort in diagnosing potential underlying causes and other medical correlates.

As to the specific complaint of fatigue, a wider variety of conditions correlated with fatigue, and a subjective variability in impression and expression of this complaint makes it often difficult to properly identify, diagnose, treat, and manage.

Sleep disorders

Poor nocturnal sleep is generally associated with daytime sleepiness regardless of the underlying sleep-disrupting condition. Both men and women have a two-to-three-fold increased daytime sleepiness if they have frequent awakenings during the night, or problems falling back to sleep once they wake up [1]. There are a number of conditions that cause sleep disruption. They could manifest primarily in increased daytime sleepiness (for example, nocturia, stroke, neurodegenerative illness), fatigue (for example, cancer, hepatic conditions, nocturnal frontal lobe epilepsy) or both (for example, hormonal imbalance, pain syndromes, multiple sclerosis, systemic lupus erythematosus, anemia).

In addition to general medical disorders, this population tends to also suffer more from primary sleep disorders causing daytime sleepiness and fatigue. Among these, sleep disordered breathing (SDB)/sleep apnea is certainly a leading example. SDB appears both as an age-related and an age-dependent condition [7]. The prevalence of SDB as an age-related disorder peaks in middle to older middle-age (and not older age). However, as an age-dependent condition, the prevalence continues to rise throughout the aging process, and this accounts for the slow and steady rise that is observed in elderly populations. The incidence in the non-obese population is relatively small – there is an increase of approximately 2 respiratory events per hour of sleep over a 5-year period, as measured by

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the apnoea–hypopnoea index (AHI) [8], and it is slightly higher (<4 events/hour) in the moderately obese. In individuals who suffer from SDB, daytime sleepiness is a common symptom, often confused with symptoms of mental decline and impairment in patients who suffer from equally prevalent neurological disorders characteristic for the same age group (such as dementia), or hypersomnolence in psychiatric disorders (such as depression). Generally, untreated SDB in the elderly is considered to be a lesser contributor to mortality than in the younger middle-aged population. This notwithstanding, the consequences are serious enough to merit treatment, especially since the elderly respond equally well to the conventional treatment, as compared to younger patients.

Less frequent as a cause for daytime sleepiness, but highly prevalent in the elderly population, are movement disorders, most importantly restless legs syndrome (RLS) and periodic limb movements in sleep (PLMS). Both of these conditions are associated with poor overnight sleep, which generally results in an increased daytime sleepiness. However, it appears that the impact of PLMS, including the arousability and an autonomic activation associated with leg movements, is less prominent in the elderly, compared to younger patients. On the other hand, in the elderly population RLS remains a common and significant condition that affects the initiation, consolidation, and continuity of overnight sleep, which all could result in daytime sleepiness and fatigue. RLS in the elderly population can be associated with decreased iron levels in the cerebrospinal fluid in chronic fatigue syndrome (CFS), despite sufficient serum ferritin and CNS prohepcidin levels (iron is required for dopamine production, while hepcidin regulates iron release, and could be deficient in younger RLS patients)[9]. This suggests that there may be an active compensatory mechanism that, teleologically, tries to preserve CNS intracellular iron levels. The higher incidence of RLS in the elderly population in connection to ferritin deficits may also be related to specific age-related conditions, such as iron deficiency in anemia caused by a colonic cancer, which is more often seen in the elderly. RLS may also be related to other conditions that are associated with an advanced age, such as neuropathies or kidney failure. It is important to note that treatment for PLMS and RLS (dopamine agonists and sometimes benzodiazepines such as clonazepam) may contribute to daytime sleepiness, while medications given as a treatment for other medical conditions could exacerbate nocturnal movement disorders (for example, antidepressants).

Narcolepsy is a sleep disorder characterized by, amongst other symptoms, irresistible sleep attacks resembling spontaneous napping in elderly. It is, however, very unlikely that (previously undiagnosed) narcolepsy presents for the first time in old age. On the other hand, the clinical presentation resembling that of narcolepsy, including uncontrollable sleep attacks, cataplexy, and sleep paralysis, could be seen in patients with multiple sclerosis [10]. In contrast to narcolepsy patients, there is no decrease in levels of hypocretin, and the genetic markers in these patients and, to a high degree, objective EDS markers are negative.

Psychological considerations

While there are a number of sleep disorders that feature various levels of sleep disruption that are associated with objective daytime sleepiness, some complaints, most notably insomnia, lack this association. A number of studies have demonstrated that patients with insomnia may have significantly disrupted overnight sleep, and yet no significant objective daytime sleepiness as a consequence. It is not uncommon for such patients to report subjective daytime sleepiness and/or fatigue, in addition to a variety of decrements in daytime functioning. One has also to keep in mind the possibility of a multi-etiological nature of the problem, when it comes to diagnosing and managing non-restorative sleep. After taking into account different medical disorders, psychological issues, medications used, and physiological changes, what remains is a very small percentage of patients who suffer from primary insomnia, and whose fatigue (and less often sleepiness) can not be linked to a comorbid condition [11, 12, 13]. Special consideration should be given to situations where a patient reports a good night's sleep and denies excessive daytime sleepiness, while the supporting evidence, including a spousal report, suggests otherwise. A recent study identified that a small proportion of patients overestimates their overnight sleep, which is objectively insufficient and not fully restorative. As a result, they show excessive daytime sleepiness on objective testing, of which they are typically not aware [14].

Special consideration should be given to mood disorders in the elderly population, and in particular depression. While still considerably prevalent, major

depression shows a mild trend of decline as age progresses from sixties into seventies, and than further into eighties. The frequency of symptoms of minor depression (conditions such as dysthymia, cyclothymia, or minor depressive episode) may actually mildly increase with an advancing age, but this remains a point of debate. Depression is more frequent in women of this age group. Mood changes affect sleep (and vice versa), mostly as different forms of insomnia, but they could also manifest as excessive daytime sleepiness. The latter was primarily associated with depression in younger patients, or patients who suffer from bipolar disorder; new evidence suggests that the elderly may also feature EDS as part of the depression symptomatology [15], possibly related, at least in part, to genetic predisposition [16]. Typical depression presentation in elderly patients may also involve specific elements, such as excessive rumination about health, loss of partner, death (including dying in sleep), or debilitating illness. Depression may present in the form of increased irritability, resentment, ahedonia, or loss of interest for daily activities.

Owing to the overlapping symptoms, it is often difficult to delineate between different disorders with similar (initial) presentation – the example for this is EDS in a patient with snoring, mild cognitive decline, and general loss of interest. In such a case, a clinician would need to carefully screen for sleep apnea, dementia, depression, and circadian rhythm disorder, among other disorders.

Hughes and Bliwise [17] have investigated a relationship between EDS/fatigue, depression, and sleep apnea, and their causal and reciprocal relationship in the non-clinical elderly population. They have found a relationship between fatigue and both sleepiness and depression, as well between SDB and EDS, but not between EDS and depression, or between SDB and fatigue, and SDB and depression. They have also found that women had higher depression scores, but less report EDS and fatigue. The implication is that, in the non-clinical population, these conditions seem to be better delineated. A possible explanation for such lack of association could be that the overlap of symptoms presents a characteristic of respective stage-advanced conditions, particularly SDB [2, 18]. The results of this longitudinal study [18] showed co-occurrence of depression and SDB, worsening of symptoms (stage-advancing) of both conditions over time, and a synergistic relation (dose-dependence) between these conditions, suggesting potential clinical implications (for example, that treating SDB could improve symptoms of depression). Another study [19] demonstrated not only a clear association between SDB and depression in obese patients, but also between depression, SDB, and EDS. In this study, unlike the positively identified association with depression, EDS was not associated with metabolic markers typically seen in SDB. Furthermore, the co-occurrence of EDS and depression, and to a high degree SDB, in association with a number of other medical disorders prevalent in older age (neurodegenerative diseases, stroke, dementia, systemic lupus, etc.) should always be considered.

Age-specific considerations and disruption of circadian rhythms

By virtue of the physiological decline in overall function and health, the frailer of the elderly population are more likely to live in an assisted-living facility or nursing home. Prevalence of sleep disorders and in particular daytime sleepiness and fatigue are even higher in this specific elderly population. Daytime sleepiness is, for example, 50% more frequent in the elderly who live in an assisted-living facility as compared to the non-institutionalized elderly population. This observation may be related predominantly to depression and poor health in general. Additional factors that affect sleep disturbances in this population are dampening of physiological sleep cues (light, activity, mobility) and environmental factors that may affect overnight sleep (noise, increased intensity of artificial light), resulting in increased daytime sleepiness. Both the maladaptive behavioral changes and physiological changes of circadian rhythms in the elderly population may result in an increased incidence of advanced sleep phase, as well as the disruption of the normal 24-hour sleep distribution [20].

When juxtaposing different findings in the elderly population pertaining to changes in sleep architecture, the specifics of the targeted population must be taken into account. Different studies with contradictory findings have studied different elderly populations ("healthy aging" vs. "institutionalized aging"). For this reason some studies show that the elderly population may or may not have a decline in sleep duration, sleep efficiency, and sleep quality, or increase in wakefulness after sleep onset [21, 22]. At the same time, a number of studies have shown universal changes in circadian rhythms related to aging. The

most robust circadian markers are advance of the circadian cycle and decrease in ability to tolerate rapid shifts in sleep phase. Some of the studies also suggest flattening of circadian amplitudes and a decrease in melatonin production. As to the latter, it is feasible that melatonin exceeds its sole role in circadian rhythms regulation, and that its decline in secretion could also be related to different age-related diseases (ultimately affecting sleep) through its antioxidant and free-radical suppressing role. It is also important to note that neither the change in circadian markers nor the decline in melatonin secretion is age specific and thus reserved only for the elderly population. These changes can occur throughout the adult life cycle, often being more prominent during earlier life stages.

Medications and alcohol

The elderly are more likely to use multiple medications, and some of them could have an impact on daytime sleepiness and fatigue. This can be either a direct or a carry-over effect of a drug (for example, benzodiazepines, levodopa/dopaminergic agents), or a consequence of interrupted overnight sleep (e.g. diuretics) [23]. Often a clinical situation may involve multiple etiological factors in addition to the medication use, contributing to daytime sleepiness and fatigue. Pain syndromes requiring use of morphine or morphine derivative is one such example. This situation may become even more complicated when other conditions (e.g. depression) or different medications are introduced into the equation [24].

Aside from medications, alcohol remains a ubiquitous factor affecting sleep in this age group; ethyl alcohol (EtOH) has a mild hypnotic effect that wanes as its blood concentration decreases, resulting in increased terminal sleep fragmentation and increased wakefulness. When taken during the day, EtOH may cause excessive daytime sleepiness. In addition to this, elderly people, when compared to younger individuals, usually reach higher blood and CNS concentrations after consuming an equal dose of alcohol. Long-standing drinkers do not appreciate that they are physiologically changing and tend to discount the possible role of alcohol in their daytime function.

Chronic fatigue

A specific complaint of chronic fatigue could be associated with a relatively poorly defined host of conditions that includes CFS, fibromyalgia (FM), and chronic widespread pain (CWP). These conditions are considered significant from the point of view of a sleep clinician because they often feature some form of sleep disruption (typically non-restorative and fragmented sleep, often described as "being asleep and awake at the same time"). Fatigue seen in these conditions can be described either as mental fatigue, mental exhaustion, tiredness, or inability to focus on a particular task (central fatigue) or physical exhaustion, lack of energy, or need to rest (physical fatigue). An important distinction between such fatigue (both mental and physical) and physiological fatigue caused by physical effort is that the former is not significantly improved by rest. In the situation where fatigue is combined with physical symptoms of musculoskeletal pain, soreness, or tenderness, a provisional diagnosis of fibromyalgia or chronic fatigue syndrome are often used to label the condition. These conditions usually (in up to 80% of patients) involve some form of sleep disruption and diurnal variations in symptom intensity (mornings and evenings being the worst in terms of the fatigue and functional ability to perform usual tasks). At the same time, such subjective perception of inadequate sleep does not always correspond with the objective findings. When compared to normal controls, little or no discernable differences were found [25]. This could, however, mean that we do not as yet have a reliable parameter by which we can measure and compare when assessing the quality and perception of sleep. Further illustrating the point, a polysomnographic marker commonly used to identify fatigue and pain – a substantially raised activity in the alpha range of the EEG spectrum and intrusions of alpha EEG activity into delta EEG activity – has not been consistently shown to differ significantly between patients with chronic fatigue/fibromyalgia and normal controls [26, 27, 28].

The complaint of fatigue is quite frequent in an institutionalized elderly population (98% report some degree of fatigue, 7% severe fatigue) [29]. A specific consideration regarding fatigue in the elderly is that the condition of chronic and persistent fatigue often fluctuates and does not improve over time to any significant degree, in spite of various treatment strategies that are typically considered. As for the sleep complaints, the symptoms may actually deteriorate over time. Over a period of years, patients with chronic fatigue report an increase in both the complaint of non-refreshing sleep and difficulty initiating or maintaining sleep. Again, as previously mentioned, these

complaints are typically not corroborated by objective tests (25). There is also an increase in the incidence of chronic fatigue and sleepiness related to the menopause, both at the time of the menopause onset and during its course [30]. As shown in elderly female patients, symptoms of pain (both as FM and CWP) may also increase over the years. In comparison to this relatively longitudinal trend, EDS shows a V-shaped curve, with peak levels of daytime sleepiness in adolescence and old age (particularly high in those who are older than 75 years) [7].

Treating excessive sleepiness and fatigue

The first step that one should consider when encountering an excessively sleepy or tired patient is to establish the semantic principles and consequently determine if the patient and his or her physician are using the same terms to describe the nature of the complaint. Terms such as "sleepiness," "fatigue," "drowsiness," and "tiredness" are used interchangeably in the general population, and one should be aware of this. Shapiro *et al.* [31] described an adjectival checklist (FACES), which tries to probe this issue.

Proper diagnostic procedures should include simple and reliable tools that will help in determining longitudinal sleep changes, a two-week sleep diary being such a tool, and temporal status through use of different scales and questionnaires (Epworth Sleepiness Scale, Stanford Sleepiness Scale, various fatigue scales). The use of actigraphy helps in corroborating the self-reported longitudinal trends. It is prudent to also utilize overnight and daytime polysomnography, particularly when assessing suspected sleep disorders or in case there is contradictory information (self-report vs. actigraphy or spousal information). In addition, an overnight polysomnography is a prerequisite for a subsequent daytime PSG test – Multiple Sleep Latency Test.

The Multiple Sleep Latency Test (MSLT) is the most reliable objective measurement of daytime sleepiness, when the patient is given four to five 20-minute opportunities to initiate a nap in a favorable situation. A mean sleep latency of less than 5 minutes is suggestive of significant daytime sleepiness, while 10 minutes suggests a normal level of daytime sleepiness. There is a reasonable level of correlation between the easily administered Epworth Sleepiness Scale (ESS) and MSLT; however, the ESS is not a substitute for MSLT [32], as it was observed that ESS scores can be influenced by psychological factors. At this point, the MSLT is regarded by many as a gold standard in the diagnosis of excessive daytime sleepiness. This said, it is important to note that motivation can delay sleep latency during the MSLT, but the reverse is not true [33].

Important factors determining the need for treatment of EDS include chronicity, severity, reversibility in response to adequate overnight sleep, resistance upon demand, impairment of daytime functioning, and danger of (self) injury.

When the cause of daytime sleepiness and fatigue lies in an accentuated physiological change, in maladaptive behavior in response to life events, or in poor sleep hygiene, the cognitive and behavioral intervention is certainly a first step. A patient should be instructed concerning good sleep hygiene practices, including sufficient exposure to bright light, sustainable physical activity, reduction of excessive body weight, and avoidance of alcohol, late caffeine and heavy meals. As mentioned above, one of the important issues is timely exposure to bright light. In patients with a disruption of the sleep phase, properly timed exposure to bright light can improve or even reverse such a disruption [34]. However, this method appears to be less effective than was previously thought when administered to improve late awakenings in patients who suffer from maintenance insomnia (late evening exposure to light, in the latter case) [35, 36, 37]. By regulating the overnight sleep, use of bright light and/or melatonin can reduce levels of daytime sleepiness and fatigue.

When it comes to behavioral interventions, one of the most controversial issues is that of daytime naps. In some cultures an afternoon siesta is viewed as the norm, particularly in the elderly population. A number of studies on this issue have shown conflicting findings, with some of the divergence stemming from differences in methodology and sampling. The afternoon nap has partly a physiological substrate; a "mid-afternoon dip" represents a trough in circadian measures, including the core body temperature, coinciding with subjective sleepiness and decreased psychomotor vigilance. The amplitude of these changes is much smaller compared to the late evening dip, which leads into the nocturnal sleep.

Larger epidemiological studies suggest increased daytime napping in the elderly; at the same time, a subset of healthy elderly individuals differ little in their levels of daytime sleepiness, when compared to

younger controls. Most of the studies find daytime napping in elderly subjects beneficial when it comes to improving daytime performance and alertness, and in delaying advanced sleep phase [38, 39]. Daytime napping also improves both sleepiness and fatigue. There is an increasing body of evidence suggesting that daytime napping does not significantly affect night sleep, and that it actually adds to the cumulative 24-hour sleep duration [39]. An added benefit is the frequent improvement of mood and some physiological measures, such as a decrease in diastolic blood pressure, compared to daytime rest without sleep in the same patient [40]. On the other hand, some of the studies also suggest that daytime napping reduces overnight total sleep time and sleep efficiency, and increases sleep latency and early morning wake time, particularly when the daytime naps lasted more than 30 minutes. Longer daytime napping (>30 minutes) is also connected with sleep inertia, which can last more than 2 hours upon awakening. One has to keep in mind that the daytime napping is more frequent in individuals with other health problems, although no direct causal effect can be elicited. When it comes to advising patients whether or not to take daytime naps, one has to have in mind individual variability and the complete clinical status of a patient. After taking all these considerations into account, the health toll/benefit ratio is certainly positive in situations where there is a need for improved daytime performance and where there is an absence of impairment of overnight sleep; it is usually prudent to rely on an objective measurement to test both the overnight sleep and daytime sleepiness before approving daytime naps, having in mind often discrepant subjective information.

In addition to the physiological substrate, a higher incidence of daytime sleepiness can be found in the elderly because of changes in lifestyle. Retirement could mean less social contact, reduced physical activity, longer quiet sedentary periods, and inappropriate use of alcohol or medications. Most of these factors can be properly addressed, and the behavioral changes often result in a favorable outcome. Meaningful daytime activities (such as volunteer work or participation in social clubs), light daily exercise, restricted time for watching TV (a common sleep-inducing situation), avoidance of alcohol, bed restriction, and stimulus control all add up to improving daytime sleepiness and fatigue. It is often perceived as counterintuitive for a patient to engage in light physical activity in order to fight fatigue, when it makes more sense to take a rest, have a nap, or watch TV instead. Because of this, it could take some time for a physician to devise an acceptable behavioral treatment plan that will take into account the patient's level of mobility, stamina, interests, and social circumstances. Compliance rates (similar to those seen in cognitive therapy) are not as high when compared to pharmacotherapy, while the success rates of simple measures such as daily light exercise are often superior in comparison to medication treatment.

Cognitive behavioral therapy (CBT) and relaxation training are important elements in treating fatigue [41, 42, 43]. Different relaxation and EMG biofeedback techniques show reasonable success for improving chronic fatigue. The same is true for the CBT, although the level of effectiveness may not be as impressive. A high dropout rate (reaching up to 42% in one of the samples) [41] hindered the predictive outcome in patients who underwent CBT, which could be an indication that patients with chronic fatigue prefer a quick fix for their problem, presumably in the form of medication, rather than suggesting that the CBT has limited effectiveness (which is estimated at 50%, patients had fatigue levels within normal range at follow-up after receiving CBT).

Excessive daytime sleepiness has been primarily treated with psychostimulant medication when appearing as a cluster symptom in narcolepsy and idiopathic hypersomnia. With the appearance of newer medications, particularly modafinil, therapeutic indications have been increased to include treatment of excessive daytime sleepiness associated with other sleep disorders (shift work, sleep apnea) [44]. Older stimulants include amphetamine and amphetamine derivatives (dextroamphetamine, methylphenidate). Amphetamine and its derivatives target catecholamine release and reuptake (with an important role in regulation of dopamine transmission, which is relevant in inducing wakefulness), and their effect is not CNS specific. This makes them highly potent in promoting wakefulness, but also makes them prone to causing a variety of (central and peripheral) side effects, mostly related to noradrenergic stimulation. The majority of side effects pertain to changes in the tone of smooth muscles, affecting the cardiovascular and gastrointestinal system, and also side effects related to the CNS and autonomic system. This makes them particularly difficult to titrate in the elderly population, which is more prone to developing dysrhythmias, micturition problems, dizziness, confusion, mood changes, gastrointestinal

problems, and sleep disturbances. Pharmacodynamics of these medications is generally favorable, and there is little enzyme competition that may cause drug-to-drug interactions.

The newer "alertness enhancer," modafinil, and other medications in this group, most notably bupropion, selegiline, caffeine, and potentially sodium oxybate and selected tricyclic antidepressants with mild stimulant effect are also used to treat EDS. Specific properties of individual drugs could be used to treat co-morbid conditions – bupropion is particularly effective in treating EDS and fatigue in depressed patients, selegiline in movement disorders, etc. In terms of safety, due to the specific mechanism of action, modafinil has several advantages over amphetamine-derived stimulants. The most important safety feature is lower levels of tolerance and dependence. Equally important and pertinent to the elderly population is the paucity of cardiovascular and CNS side effects. An important feature when considering the elderly is the relative absence of neuroendocrine modulation, and, in particular, lack of effect on melatonin secretion. This makes modafinil a first-line treatment choice in populations sensitive to disruption of circadian rhythms and sleep patterns. It is important to note that modafinil interacts with some of the cytochrome P450 isoenzymes and has a potential to interact with other drugs using the same metabolic pathway. In the elderly, it is necessary to decrease the usual doses of modafinil, particularly in those patients who have hepatic conditions.

The use of caffeine as a stimulant (or rather as an "alertness/performance enhancer") is both universal and controversial. Caffeine is a rapid-acting general stimulant. The "therapeutic" (stimulant) dose of >200 mg can be found in 2–4 regular cups of coffee or tea, 4–6 colas or other caffeinated soft drinks, one or two "energy drinks," and, importantly, three tablets of Excedrin or similar drug combinations containing caffeine. Owing to its non-specific adenosine antagonistic action, excessive use of caffeine (caffeinism) produces significant side effects that include nervousness, increased irritability, tremor, insomnia, headache, heart palpitations, tachypnea, diuresis, and gastrointestinal irritation. In addition, excessive chronic use of caffeine can be associated with restless legs syndrome and REM sleep behavior disorder [45]. Studies have shown that caffeine reduces daytime sleepiness, improves daytime performance (affected by increased sleepiness), and affects circadian sleep distribution in non-habitual sleep deficit. In habitual insufficient sleep, it is suggested that chronic use of caffeine only restores levels of performance closer to the baseline levels [46].

Specific pharmacological treatment of fatigue [47] includes both the symptomatic relief and treatment of underlying conditions. Methylphenidate was found to be effective in treating chronic fatigue in patients with cancer. Some of the studies also showed a beneficial effect of bupropion. Amantadine was found to be possibly helpful in patients with multiple sclerosis. Promising results were found with use of modafinil; however, a number of recent studies showed no significant improvement in fatigue levels when compared to placebo. Some of the specific conditions where it may be beneficial to consider modafinil in treating both fatigue and EDS are primary biliary cirrhosis, myotonic dystrophy, and Charcot-Marie-Tooth disease (with the caveat that much of the above information comes from single-site small-scale studies). There is a potential role of adjuvant use of modafinil in treating EDS and fatigue, and there are some promising initial findings in use of its longer half-life enantiomer, armodafinil. Similarly promising but inconsistent initial results were found with the use of sodium oxybate/gamma hydroxybutyrate and melatonin. Use of caffeine in higher doses (>200 mg, typically at 600 mg) was shown to abate acute fatigue.

Unfortunately, chronic fatigue does not significantly respond to placebo (<20% response rate) [48], which renders a number of traditional and alternative OTC preparations ineffective, contrary to the common belief. Such a notion is partly confirmed in a study [49] that showed that 35% of the sample with chronic fatigue reported improvement of symptoms while using the OTC/alternative medications and therapies, and half of these patients (accounting for less than 18% of the total sample) believed that these measures actually caused the abatement. Conflicting results are also reported regarding the use of D-ribose (monosaccharide involved in cell metabolism) and L-carnitine.

The majority of medications currently in use for treatment of EDS and fatigue modulate catecholaminergic pathways (it was also suggested that modafinil has a GABA-suppressing effect). Novel and future medications may focus on hypocretin, and specific glutamatergic, histaminergic, and GABA/adenosine-suppressing mechanisms, which may decrease a number of side effects and widen the spectrum of therapeutic indications.

Addressing underlying sleep disorder or other physical conditions, and dealing with psychological issues is certainly a necessary step in treating co-morbid EDS or fatigue. In a certain number of patients such treatment may not completely eliminate EDS, and in such cases residual sleepiness can be treated with adjuvant stimulants; a good example is treatment of residual sleepiness using modafinil in obstructive sleep apnea initially treated with CPAP. Even in cases where fatigue and EDS are primary complaints, treatment of underlying conditions could eliminate the need to specifically target these two complaints. For example, in cases of anemia or hormonal imbalance, frequently seen in the elderly population, supplemental and replacement therapy often significantly improves fatigue.

Conclusion

Excessive daytime sleepiness and high levels of fatigue in elderly subjects often heralds a broad number of medical disorders. On the other hand, healthy aging is typically void of elevated sleepiness and fatigue; a message that needs to be conveyed to physicians and patients alike. A correct diagnosis is an important step, and one must try to tease out the specific complaint, as the fatigue and EDS do not necessarily coincide [50, 51]. Such discrimination may also help in diagnosing a potential underlying sleep disorder and thus facilitating an effective treatment. A treatment plan of excessive daytime sleepiness and fatigue needs to address the often multifactorial nature of the problem [52, 53]. When managing primary EDS and fatigue, one must consider every avenue of treatment, from simple and easily administrable behavioral and cognitive interventions, to supplemental and replacement therapy, to specific medication regimens tailored to the individual patient's needs.

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Part 3
Chapter
28

Sleep disorders in the elderly

Sleep and falls in the elderly

Stephanie A. Studenski

Introduction

Falls are a serious problem among older adults because they are common, disabling, and sometimes fatal [1]. Among older adults, falls are frequently due to an accumulation of abnormalities in body systems that control balance [2]. The causes and management of falls and balance disorders are high-priority areas for aging research and clinical care, but the potential contribution of sleep problems to falls has received little attention. Clinical guidelines for evaluation and management of falls have not included any aspect of sleep other than the use of sedatives [3]. Emerging evidence suggests that sleep disorders of aging may contribute to falls in ways that are independent of sedating medications. The goals of this chapter are to provide an overview of the effects of aging on balance and falls, to explore potential mechanisms by which sleep disorders might affect balance and falls, to present evidence about the contribution of sleep disorders to falls, and to propose opportunities for future research.

What is known about the causes of falls?

The loss of the ability to move with confidence has implications for independent functioning and risk of injury. Thirty to forty percent of community-dwelling adults over age 65 experience at least one fall each year, with rates increasing after age 75 and in persons who live in nursing homes [1, 2]. About 5% of falls result in serious injuries such as fractures [1, 2]. Falls can be fatal; unintentional injuries are the fifth leading cause of death in older persons and two-thirds of these injuries are attributable to falls [4]. Less obvious, but potentially of major significance, is the effect of falling on self confidence and activity. Fear of falling can result in restricted activity, reduced mental well being, and social isolation, and can contribute to a vicious cycle of declining health, disability, hospitalization, institutionalization, and death [5].

Epidemiological evidence about risk factors for falls is based on principles of cumulative risk. Among older adults, most falls have multiple contributing factors and a single overall cause for a fall is rarely identified. Table 28.1 describes possible dominant contributors to falls according to a recent summary review [6]. Of course, a history of falls is a consistent risk factor. Other well-documented intrinsic risk factors include gait and balance problems, lower extremity weakness, vision problems, dizziness, use of multiple medications, cognitive disorders, use of assistive devices, and foot problems [1, 6]. Environmental, behavioral, and person–environment interactions are also important [7]

Balance or postural control is the ability to remain upright in motion. It is dependent on highly refined interactions among multiple systems, consisting of sensory inputs, central nervous system processing, and effector outputs [8]. The main sensory contributors are visual, vestibular, and somatosensory functions. CNS contributors are difficult to classify but could be considered to include any process that affects cerebral perfusion (e.g. hypotension, arrhythmias), factors that affect attention, reaction time, or executive cognitive functions such as visual-spatial abilities or planning and sequencing activities (possibly attributable to sedatives, hypoxia, or some cognitive disorders) and factors that directly affect postural responses (e.g. Parkinson's disease). The main effector factors within this model are muscle (strength, speed of contraction and fatigue), joint range of motion, and cardiopulmonary endurance (Table 28.2). Systems can compensate or adapt to impairments in other systems. For example, a person with low vision can move with confidence by depending more on sensory input from vestibular and somatosensory systems.

Balance fails when the demands of the movement task are greater than the resources available from across the components of postural control. Balance may appear to be intact when an individual routinely limits exposure to more demanding tasks or when there is

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Table 28.1. Epidemiological risk factors for falls

30%: accidents/environmental causes
17%: poor gait and balance
13%: dizziness
9%: drop attack
5%: confusion
3%: positional hypotension
2%: visual disorder
<1%: loss of consciousness
15%: other specific causes
5%: unknown

Adapted from [6].

Table 28.2. Systems that contribute to human postural control

Sensory
Visual
Somatosensory
Vestibular
Central nervous system
Vascular perfusion
Alertness and attention
Executive cognitive functions such as visual-spatial ability, movement planning, and sequencing
Reaction time
Automatic postural reflexes
Effector
Muscles
Joints
Cardiopulmonary endurance

effective compensation for a deficit in a component of postural control, as described above in the case of low vision. Thus the postural control system should be considered to have substantial "physiological reserve," or excess capacity, that is only called upon when the task is challenging or when system impairments accumulate and compensatory resources are needed. Thus, detection of balance capacity must incorporate a range of biomechanical difficulty, extending into tasks that are challenging for the individual.

Biomechanical studies of balance and falls are based on concepts of mass, force, and motion. To stand upright, the human must control a "tower" or tall narrow mass over a small base of support. To move, the human must displace and recover this tall column of mass over a moving base of support. Biomechanical assessments can include both "static" tasks in which the base of support does not move (for example, sway and standing balance) as well as "dynamic" measures in which the base of support displaces and recovers (for example, stepping, tripping, slipping, and walking). The biomechanical task can vary in difficulty based on the speed and complexity of motion and the size of the base of support. Thus, lying and sitting are simple balance tasks, standing and walking are somewhat more challenging, and standing on one foot or walking heel to toe are more difficult. Typical human movements, such as walking, stair climbing, rising from a chair, or recovering from a slip or trip, have been well characterized biomechanically. Studies of aging from a biomechanical perspective report increased body sway [9, 10], slower reaction times [11, 12], decreased toe clearance [13], and increased variability in stepping patterns [14, 15, 16]. Biomechanical alterations can also be used to classify types of abnormal balance and can sometimes be linked to specific physiological impairments. For example, persons with peripheral neuropathy, a common form of sensory impairment in older people, may demonstrate a wide base of support, increased trunk sway, and a tendency to increase toe clearance due to inability to sense the weight-bearing surface while walking [16].

The recent focus on the need to stress balance in order to detect subtle abnormalities has led to concepts and paradigms that test the effects of varying conditions on static and dynamic balance, and on fall risk. One approach, often used in posturography, alters access to visual and somatosensory information and determines the effect of varying conditions on sway [17, 18, 19]. Another set of paradigms stresses balance by presenting cognitive and movement tasks separately and then together, often termed "dual tasking" [20, 21]. Fall risk may be higher when performance worsens substantially when additional tasks are added. Recent literature suggests that the type of cognitive task, e.g. whether it involves verbal memory, calculation, and/or image visualization can impact movement performance [22, 23]. Such approaches can identify older adults at increased risk of balance problems, and are especially sensitive to subclinical deficits such as mild cognitive impairment or subtle vestibular dysfunction.

When assessing the causes of a balance problem, occasionally a single causative pathology may be found. More often, a balance problem is due to an accumulation of deficits across the components of postural control. For example, a classical case of poor balance in an older adult is an individual who appeared to have adequate balance despite low vision and peripheral neuropathy, but became a faller when reaction time slowed as a consequence of a sedative medication. The concepts of physiological reserve and compensating systems as keys to successful balance have important implications for the potential role of sleep disorders in falls.

Potential mechanisms by which age-associated sleep disorders might affect balance and contribute to falls

Sleep disturbances of aging, especially self-reports of difficulty starting or maintaining sleep and/or of daytime sleepiness, as well as objective measures of altered time in deeper sleep stages, increased arousal rates, and sleep disordered breathing (SDB) are common among older adults [24, 25, 26, 27]. These sleep disturbances of aging have the potential to be frequent but unrecognized contributors to balance disorders and falls. Sedative use is a well-established, strong, and consistent risk factor for falls [28, 29, 30], but little is known about whether the sedatives themselves are the primary contributor or whether sedative use is, at least in part, a marker for a population with sleep problems.

One of the most obvious mechanisms by which sleep disorders might contribute to falls is by reducing alertness and attention (Table 28.3). While this phenomenon is often proposed, there are surprisingly few data to support it. There are some studies in healthy young adults of the effect of sleep deprivation on sway using posturography, but none on older adults [31, 32]. A recent study found no effect of nocturnal awakening on sway in healthy older adults [33]. Alertness and attention can vary over time and are affected by common health conditions of aging such as hypotension, hypoxia, and congestive heart failure. Thus the interaction between sleep and attention might vary over time and might be especially problematic in populations with multiple contributors to poor attention. This is the most obvious mechanism by which sedatives, daytime sleepiness from any causes, insomnia, and sleep disordered breathing might contribute to falls.

Multiple executive functions such as visual-spatial accuracy, psychomotor speed, planning, and sequencing, are important for dynamic balance [34]. Executive dysfunction is associated with disorders such as hypertension and atherosclerosis, which contribute to cerebrovascular ischemia and so-called "white matter small vessel disease" seen on magnetic resonance imaging [35, 36]. The potential contribution of sleep disordered breathing to impaired executive function and cerebrovascular ischemia is an area of active investigation and there is substantial disagreement in the literature [37, 38].

Orthostatic hypotension can contribute to falls largely via transient dizziness and decreased attention. Orthostasis tends to be worse after prolonged inactivity and/or lying in a recumbent position. It is possible that napping or long sleep leads to transient periods of increased orthostasis, although again, there is little actual evidence to support this concept. Orthostatic hypotension is also a manifestation of autonomic dysfunction. Since autonomic dysfunction and hypotension have been proposed by some investigators to be an element of sleep disordered breathing, it is possible that some sufferers have transient periods of increased orthostasis [39]. There is little clear evidence to support this potential effect.

Deconditioning with inactivity affects balance through effector factors like flexibility, muscle strength, and aerobic capacity. Older adults with daytime sleepiness due to sleep disordered breathing or insomnia may be less physically active [40]. Conditioning exercises that include strengthening and endurance along with formal balance exercise are considered mainstays of interventions for falls [41] and may be useful for older adults with inactivity associated with sleep disorders.

Finally, nocturnal conditions such as low levels of light can contribute to falls, especially in persons with sensory deficits and other problems with components of postural control. Persons with insomnia or fragmented sleep who are up and about at night might be more exposed to low light conditions. Night-time

Table 28.3. Potential mechanisms underlying fall risk in sleep disorders

Reduced alertness, attention and psychomotor speed: transient and chronic
Executive dysfunction
Orthostatic hypotension
Deconditioning
Night-time activity under low sensory information conditions

lighting is considered an important environmental modification for persons with fall risk [1].

Evidence for sleep disorders as risk factors for falls

Recent cross-sectional and prospective observational studies have confirmed an association between general sleep problems among older adults and falls (Table 28.4). The quality of measurement of sleep and falls varied among the studies. Findings related to types of sleep problems are inconsistent in that some studies find greater associations with night-time sleep problems [42, 43], while others find more associations with daytime sleepiness [44]. Some studies found associations with longer sleep [45], while others found relationships with shorter sleep [46]. Several studies were able to control for sedative use and found sleep–fall associations that persisted, suggesting an independent contribution from sleep problems beyond the effects of sedatives [45, 47]. Two recent studies have specifically examined the relationship between sleep disordered breathing and falls. Self-reported physician diagnosis of sleep apnea was associated with fall history [55]. Polysomnographic evidence of sleep disordered breathing was associated with recurrent falls in women but not men [48].

There are very few physiological studies of sleep and balance in the elderly. There are reports of the effect of sedatives on sway [49]. A recent large epidemiological study confirmed independent relationships between sedating drugs and clinical balance measures [50]. Another study found that multiple central nervous system active drugs especially increase fall risk [51]. A single recent study describes the lack of an effect of night-time awakening on posturographic measures of balance in healthy older adults [33]. There is evidence that sleep deprivation does affect posturographic measures in healthy young adults, but no data yet on the effect of age [32].

Similarly, there is not yet a clinical trials evidence base about the impact of treating age-related sleep problems on balance and falls. One study of a multimodal intervention to improve sleep in nursing homes showed reduced daytime sleepiness and improved physical activity but did not report on balance or falls [52]. Another recent small study describes a potential benefit on fall risk of treating older adults with subjective memory problems with methylphenidate, but there are no comments about sleep or sleepiness [53]. For sleep apnea in older adults, continuous positive pressure treatment has been shown to affect multiple factors that influence fall risk, especially alertness and executive function but there are no reported clinical trials that directly assessed balance or falls [54].

Gaps in knowledge and opportunities for further research

There are compelling reasons why older adults would benefit from a research focus on sleep and falls. Both are common conditions with multiple adverse effects. The evidence to date strongly supports sleep problems as potentially modifiable contributors to balance disorders and falls, independent of their contribution to sedative use. We need to know how sleep disorders affect balance, who is at risk for balance impairments in the presence of sleep problems, and how to prevent and treat sleep-related balance problems.

In order to move forward in this important area, we need to create conceptual models that can depict how sleep might affect balance and falls, and then use these models to examine mechanisms and develop interventions. One approach to a conceptual model is presented in Figure 28.1. In this model, there are multiple types of sleep disorders. They have both shared and unique mechanisms by which they may contribute to poor balance and falls. All forms of sleep problems are likely to contribute to two major pathways to poor whole body balance: through decreased attention and through inactivity and deconditioning. Sleep disordered breathing may have additional pathways through hypoxia and executive cognitive dysfunction, and through autonomic dysfunction and orthostasis. No matter what the main pathways are, the effect on the individual's overall balance may depend on what co-existing impairments they have in systems that contribute to postural control. Nocturnal activity may affect exposure to fall risk, especially in persons with inattention and other reasons to have poor balance.

State-of-the art methods of research in sleep and in balance can be applied to future observational, physiological, and intervention studies. We especially need to update the measurement of falls and balance in sleep studies and conversely improve the measurement of sleep in falls and balance studies (Table 28.5). We can use the next generation of epidemiological and physiological studies to better characterize risk factors and mechanisms. We could begin to include balance and falls as outcomes in intervention studies for sleep problems and could begin to assess the impact

Table 28.4. Epidemiological evidence for sleep disorders as risk factors for falls

Study/year	Design and sample	Measures of sleep	Measures of falls	Main findings
General sleep problems				
Brassington *et al*. 2000 [42]	Cross-sectional telephone survey N = 1525	Self-reported night-time sleep problems and daytime sleepiness	History of falls in the last year	Night-time sleep problems but not daytime sleepiness was associated with falls in multivariate analyses
Teo *et al*. 2006 [44]	Cross-sectional N = 782	Self-report of daytime sleepiness using Epworth Sleepiness Scale, self-report of night-time sleep problems	History of falls	Daytime sleepiness but not night-time sleep problems were associated with falls (OR 2.05)
Latimer Hill *et al*. 2007 [43]	Cross-sectional N = 300 (150 each in an Internet survey and a residential aged care setting)	Self-reported sleep and sleepiness	History of falls in the last year	Aged care setting group: history of falls associated with poor sleep quality (OR 4.5) and >2 nocturnal awakenings (OR 2.7) Internet group: persons with no reported sleep disturbance had a reduced risk of falls (OR 0.3)
Avidan *et al*. 2005 [47]	Prospective secondary analysis of statewide nursing home data N = 34 163 nursing home residents	Nursing home report via minimum data set of insomnia and sedative use	Prospective report via minimum data set of falls or hip fracture	Insomnia but not sedatives were associated with falls and fractures in multivariate analyses
Stone *et al*. 2006 [45]	Prospective cohort N = 8101 women	Self-reported sleep and nap habits	Prospective falls query every 4 months for 1 year	Multiple falls associated with >10 hours of sleep over 24 hours (OR 1.5) and daily napping (OR 1.62) in multivariate models
St George *et al*. 2008 [46]	Prospective N = 169 for falls component of a larger study	Self-reported sleep quality, napping	Prospective monthly fall diaries	Multiple falls were associated with napping >30 minutes (OR 3.1) and sleeping <6 hours (OR 3.13)
Sleep disordered breathing				
Kaushik *et al*. 2007 [55]	Cross-sectional substudy N = 1952	Self-reported physician diagnosed sleep apnea	History of falls	Multiple falls associated with sleep apnea (OR 2.02)
Studenski *et al*. 2007 [48]	Cross-sectional N = 1107	Polysomnographic confirmation of sleep disordered breathing (SDB) by RDI >15	History of falls	Multiple falls associated with SDB in women (OR 1.97) but not men (OR 1.27)

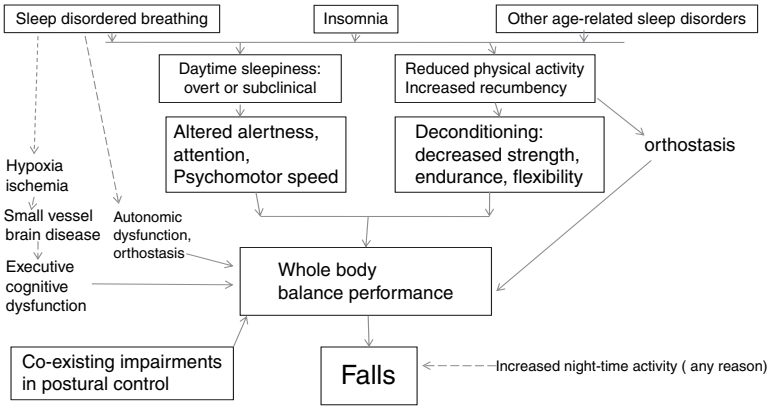

Figure 28.1. How sleep problems of aging contribute to falls.

of sleep interventions as novel additions to trials of multifactorial falls prevention. This future research will require novel collaborations and teamwork among experts in aging, sleep, and balance.

Table 28.5. Research issues and opportunities

Issues and gaps in knowledge
How does abnormal sleep affect falls and balance?
Are there populations in whom sleep disorders are more likely to precipitate falls?
Does treatment for sleep disorders improve balance and reduce falls?
Methodological approaches
Epidemiological studies
Prospective studies
Objective and self-reported measures of sleep
Objective and self-reported measures of balance
Falls ascertainment
Physiological studies
Measures of transient alterations in attention and balance during waking and sleepiness in healthy and at-risk elders
Multiple indicators of sleep physiology
Multiple indicators of balance performance at multiple time points
Measures of existing deficits in components of postural control
Clinical trials
Effect on balance and falls of treatments for:
Insomnia
Sleep disordered breathing
Daytime sleepiness
Include interventions on sleep in multifactorial interventions for falls

Summary

While assessment of sleep has not yet been incorporated into clinical guidelines for falls prevention, sleep disorders are likely to be modifiable contributors to balance problems and falls in older adults. Multiple potential mechanisms are possible; transient and chronic effects of poor sleep on attention and alertness are the most likely direct consequences related to balance. There is now emerging an exceptional opportunity to identify and test potential new effective interventions to reduce falls through interventions on sleep.

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Part 3
Chapter
29

Sleep disorders in the elderly

Dreaming and dreaming disorders in the elderly

Milton Kramer

The personal, inner world of the elderly has not been the focus of great interest to dream researchers or geriatric physicians. Klein [1] observed in 1980 that the dreams of the aged have been rarely studied. Cohen [2] in an editorial in the *American Journal of Geriatric Psychiatry* in 1998 found it remarkable that so little attention has been paid to the dream life of the elderly. He was of the opinion that "attention to dreams… presents opportunities for both identifying health problems and fostering health promotion." He observes that changes in dream content or dream experience, e.g. nightmares, may reflect disturbances related to medication side effects and that systematic dream observation, i.e. by keeping a dream diary, may suggest to the older person new approaches to problems and thereby promote a healthier lifestyle.

There has not been a systematic life cycle approach to the study of dream content. Erikson's [3] offering of a life cycle schema based on age-specific adaptive demands led to an extension of the Freudian psychosexual stages beyond latency, but the focus that came out of his effort was an interest in the vicissitudes of identity formation in adolescence. Jones [4] reworked and amplified Erikson's schema and offered a rating system to categorize dreaming by life cycle stage, again focusing on the adaptive demand of each life stage. Unfortunately, there has never been a thorough application of Jones' rating system.

There is a small literature on dream content changes across the life cycle, and despite its being limited it does suggest a developmental process. Regrettably, in the present context, the most well-studied age group using laboratory dream collection is Foulkes' [5] studies of children, ages 3–5 to 13–15. The standard reference for normative dreaming [6] is based on five spontaneously recalled dreams of 200 college-aged individuals; a reliable and reproducible reference, but with limited generalizability. A more representative population of adults between the ages of 21 and 65+ was asked to report a dream [7], and clear age-related dream content differences were reported. The small sample size (182) and the study not having been independently replicated limit the value of the results as a normative standard.

It is apparent from an earlier review [8] that studies of non-laboratory collected dream content do indeed change with age and not always linearly. Several studies described findings consistent with Erikson's life cycle stages [4, 9, 10, 11, 12, 13, 14]. The most striking dream content change was found for the intensity and manner of expression of aggression/hostility [15]. Children's dreams tend to be low in hostility/aggression and the dreamer is more likely to be an observer than a participant. Aggression/hostility increases in adolescence and adulthood and the dreamers are more likely to be a participant in rather than an observer of the aggression/hostility [16]. In old age, aggression/hostility decreases and the dreamer again is more likely to be an observer than a participant in the hostility/aggression. Elements of the fear of death appear in the dreams of the elderly [7] and many elderly dreamers see themselves as lacking in resources, weak, vulnerable, and helpless [17, 18]. Any life cycle study of dreaming must collect and report the dream content of both genders, given the repeated observation that men and women report clearly different dream content [6, 7, 19, 20].

I collected the literature on the dreams of the elderly by doing a PubMed search with the descriptors dreaming and aging. I added those articles related to aging that were cited in the tables in *Dimensions of Dreams* [8]. References cited in all of the articles obtained were reviewed and articles with titles suggesting data on dreams in the elderly were added to the group to be reviewed. I then extracted the findings from this group of articles that had findings related to whether there was or was not dream content change with the dreamer being older.

Dream recall

The appropriate place to start a review of dreaming in the aged is to see if the recall of the experience is

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altered in older individuals. Ramsey [21] in his pre-REM review of the dream literature reported that older subjects reported decreased dream recall compared to younger subjects. Strunz [22] in a literature review of dreaming in those over 50 also reports a decreased dream recall rate. In a questionnaire survey of 1200 alumni of a university, Zepelin [23] found that for the 60% or so who responded, with about two-thirds being men, those over 50 reported a lower dream recall frequency than those under 50. Herman and Shows [24] studying both men and women found a decrease in recall with age that begins in the early 30s associated with a decrease in interest in dreams that starts in the middle years. Funkhouser *et al.* [25], in a remarkably thorough review of the literature on dreaming in the elderly, concludes that the frequency of dream recall declines with age in those over 65 in both men and women, more so in the former, but as the major decline begins in early middle age it may not be connected with aging but with other competing concerns emerging. Greiner *et al.* [26] report a modest numerical increase in the recall of dreams in older compared to younger women in a diary study. A more complex pattern in age-related dream recall was found by Winget *et al.* [7] in their stratified random sample including both men and women, namely that those between 21 and 34 and between 50 and 64 reported more dreams than those between 35 and 49 and those over 65. This pattern is somewhat similar to what Herman and Shows [24] reported of a modest increase in their 50–59 age group over their 40–49 group. Waterman's [27] was the only study that found no age-related effect on home dream recall. Giambra *et al.* [28] noted large differences in recall among elderly subjects.

The examination of the relationship of dream recall and age based on awakenings from REM sleep encompasses very few studies. Kahn and Fisher [29] reported a recall rate from REM awakenings of 55.4% for 27 male subjects with a mean age of 75 compared to the 87% for young adults usually found in their laboratory. Greiner *et al.* [26] found a lower dream recall from REM awakenings in older women. Zepelin [30] studied 58 men for two nights in the laboratory awakening them from each REM period and found that for those among the 27–46 age group the median number of dreams was 6 and for those among the 47–64 age group the median was 5, a 17% decrease. Fein *et al.* [31] obtained an 81.3% recall from REM awakenings in their older female subjects compared to 97.3% in their younger subjects. Both Zepelin [30, 32] and Fein *et al.* [31] minimize the age-related recall decrease they describe. In a study of middle-aged and elderly men with mild and severe chronic brain damage, Kramer and colleagues [33] found a numerically decreased REM recall percentage associated both with age and dementia severity. Nathan *et al.* [34] found no difference in the elderly in home dream recall related to the degree of brain atrophy.

The decrease in dream recall cannot be attributed to general memory impairment in elderly, healthy subjects [22] but can be attributed to general memory impairment in those with brain damage [33] but not necessarily to brain atrophy [34]. Herman and Shows [24] found that memory for dreams was related in their middle-aged and older subjects having a decreased interest in and lower valuation of dreaming. Winget *et al.* [7] speculate that their middle-aged and older group may be less interested in internal processes. Strunz [22] attributes the decrease in recall to a lower rate of current concerns in those over 50. Interestingly, among college-age individuals those who profess an interest in dreams and place a high valuation on dreams recall fewer dreams than their disinterested peers in a 3-week diary study [35]. Waterman [27] and Fein *et al.* [31] both found a positive relationship between visual memory and the recall of dreams, and Waterman [27] found a small non-significant effect of age on recall. Schredl and Reinhard [36] attribute age-dependent gender differences to the greater encouragement given to women to focus on and report dreams, i.e. "dream socialization." They note that verbal memory does not affect dream recall but the ability to recall emotional experiences and interest in dreams increases recall. Magee [37] has recommended that dream analysis may be a valuable addition to the older person's effort at a life review with its attendant benefit. It appears that dream recall is decreased in the older person but that the decrease may have begun well before the dreamer entered old age and may be related to a decreased interest in dreams as one grows older.

It seems reasonable to conclude at this point that dream recall is associated with the age of the subject with the relationship reflecting a negative correlation. This appears to be true whether the data is obtained from home dreams or from REM sleep awakenings in the laboratory. The decrease in dream recall with age appears to occur in both men and women in contrast to what is generally found for the content in dream

reports that are heavily influenced by the gender of the dreamer. Schredl and Reinhard [36] have found in an extensive meta-analysis a small but substantial gender difference in dream recall associated with age.

Characters

We have found [38] that the characters that appear in dream reports are often a differentiating feature of such reports. We examined studies to see if the characters that appeared in the dreams of the elderly were different from those in the dream reports of younger people. Zepelin [32] found that the REM dreams of men showed a linear decrease in family content with age with the most family-related content in those between 35 and 55. Krohn and Gutmann [39] discovered that among Navajo men the older subjects in their home dreams were more passive and less often the central actor in their dreams. Brenneis [40] described in the home dreams of older women compared to younger women 'fewer characters, a decreased gender identification of characters, and when the character's gender was identified it was more likely to be that of a family member'. He also found that the dreamer was a less central character in the older woman's dreams but more active. Kramer *et al*. [33] found more family references in his brain-damaged middle-aged patients than in the Hall and Van De Castle [6] normative data from college-aged subjects. Barad *et al*. [17] reported in the home dreams of the elderly with a chronic brain syndrome that there was a decrease in the number of characters. Zanasi *et al*. [41] showed that fewer characters appear in the home dreams of elderly compared to younger persons. Waterman [27] noted no change in the number of characters in dreams associated with aging. Smith and Hall [42], in a dream series of a single individual that spanned 50 years, noted that the frequency of references to mother remain unchanged in the subjects.

There is a strong possibility that a relationship exists between aging and a change in the character aspect of the dream report. There appears to be a decrease in the number of characters, the dreamer is less likely to be the center of the dream action, and there is an increased incidence of family references with age. Older men tend to be more passive and older women may be more active in their dreams than their younger counterparts.

Social interactions

Having characterized the change in who appears in dreams associated with the dreamer being older, attention is drawn to how the characters in dreams interact with one another. Hall and Van De Castle [6] have categorized our social interactions in dreams as being aggressive, friendly, or sexual. Certainly other categorizations would be possible but they offer a reliable and certainly meaningful system to examine the social interaction aspect of the dream experience. In our exploration of the dreams of the elderly, the question we are asking is whether the social interaction that takes place in dreams changes with the age of the dreamer?

We compared the frequency of social interactions from a group of adults selected to be representative of the adult population of a city [43] to the frequency reported by Hall and Van De Castle [6] from a college student group. Interviewers sampled the adult population verbally as part of a health survey that included 300 people, 62% over 40, who provided 182 dreams while the 200 college students, who were probably between 18 and 21, provided 1000 dreams written out by them as part of a psychology class exercise. The dreams of the college-aged group had 46% aggressive interactions, 40% friendly and 8% sexual; while the adult dreams had 20% aggressive, 18% friendly and no sexual interactions. The college students' aggressive dreams were 43% physical aggression and 57% verbal while the adult dreams were 75% physical and 25% verbal. The mode of collection, sample size, as well as the age and social class differences may account for the differences in social interaction frequency in the two studies. Hall [44] in a study of the dreams of hospitalized alcoholics acknowledges that comparisons to his student norms [6] suffer because the groups were not matched for age, marriage, or education, nor the setting in which the dream was experienced [45].

Aggressive interactions

Hall and Domhoff [46] looked at 1490 aggressive interactions that occurred in 3049 spontaneously recalled dreams collected from 1940 individuals, 963 males and 977 females, ranging in age from 2 to 80. They divided the number of aggressions by the number of characters in the dream arguing that the more characters in the dream the greater the likelihood of an interaction. They found that the relative amount of aggression decreases with age in both men and women from 0.42 in males and 0.35 in females ages 2 to 12 to 0.22 and 0.07, respectively, in ages 30 to 80. If one calculates aggressive interactions per dream without correcting for the number of characters in the dream

or the gender of the dreamer one is led to a similar conclusion: aggression in dreams decreases with the age of the dreamer, as the ratio of aggression to dreams is 0.77 for those aged 2 to 12, 0.45 for those aged 12 to 18, 0.46 for those aged 18 to 27, and 0.35 for those aged 30 to 80. Unfortunately the oldest age group spans 50 years so that the comparisons that are possible are limited.

Winget *et al.* [7] found in the adult sample described above [43] that there was a decreased frequency of aggression/hostility in the dreams of their 35–49 age group compared to their 21–34, 50–64, and 65+ age groups. Age apparently is a factor in the frequency of aggressive expression in dreams that may not be simply a linear effect.

Hall and Domhoff [46] report that men have a higher proportion of aggressive interactions with other men while females have an equal proportion with male and female characters. Waterman [27] found that middle-aged and elderly men had fewer aggressive interactions than younger men and that the changes occurred before age 60. Younger women had more aggression than middle-aged and older women [67]. Strunz [22] notes that dream content changes have occurred between 20 and 45 and those seen in the elderly compared to the young may have taken place earlier. The decrease in dream recall similarly may occur before the dreamer has reached old age.

The other observations Hall and Domhoff [46] have made are: (1) that there is more witnessed aggression in children's and older adults' dreams than those in adolescents and younger adults; (2) dreamers are more often victims than aggressors, however older dreamers initiate more aggression than they receive; and (3) female dreamers show a decrease in physical aggression with age but males do not.

It appears fair to conclude that aggressive social interactions in dreams generally decrease, as the dreamer gets older. Other aspects of the aggressive social interaction such as witnessing, victim-hood, or the effect of gender all change with the age of the dreamer.

Friendly interactions

Friendliness is a less frequent occurrence in dreams than aggression [6, 43, 47]. Hall and Domhoff [47] report that in their 3048 dreams that had 1490 aggressive acts (49%) only 711 had friendly ones (23%). They describe the friendly acts as less intense than the aggressive ones. In dividing the number of friendly interactions by the number of characters in the dream as they did for aggressive social interactions, they found the ratio higher for male than female dreamers, contrary to what one might expect. They found lower ratios in children's dreams and those of older women, suggesting an age-related change in friendliness in dreams. Without controlling for characters in dreams, the friendly interaction/dream ratio is 0.24 for men and 0.23 for women [47]. In Hall and Van De Castle's [6] normative study of college-age dreamers they found that females have slightly more friendly encounters per dream than males (0.42 compared to 0.38). Kramer *et al.* [43] found that in their adult sample only 18% of the dreams contained a friendly social interaction. This is similar to Hall and Domhoff's report [47] of 23% but considerably less than Hall and Van De Castle's college student norms [6] of 40%. Winget *et al.* [7] found no age-related change in friendly social interactions. Waterman [27] found that younger men had more friendly interactions in their dreams than older men, as did younger and middle-aged women. Hall and Domhoff [47] observed that men have a greater proportion of friendly interactions with women while women have an equal proportion of such interactions with male and female dream characters.

Friendly social interactions are less frequent and less intense than aggressive ones. There is the suggestion of a decrease in friendly interactions with age that is sex related.

Sexual interactions

Sexual interactions in dreams are only rarely reported. Hall and Van De Castle [6] found only 8% of their dream reports had sexual interaction content while Kramer *et al.* [43] in their stratified sample of adults, 18% of whom were over 65, found there were no dreams that involved sexual interactions. Brenneis [40] reported no decrease in the frequency of sexual dreams in his older women (40–75) nor did Altschuler *et al.* [18] in theirs; while Wilczoch [48] cited in Funkhouser *et al.* [25] reported that of 275 dreams collected from 59 men and women between 65 and 93, 2.5% had explicit sexual images, more from men than women. Funkhouser *et al.* [25] reported on three other studies: one from Finland [49] of 75-year-olds in which only 7 of 88 dream reports (8%) had primarily sexual content; a second from Italy [50] of dreaming in elderly people found that 50% had erotic dreams; and a German study by von Sydow [51] reported that

of women (50–91 years) asked about erotic dreams in the past year, 67% aged 50–59, 68% of those aged 60–69, 74% of those aged 70–79, and 33% of those over 80 said they had erotic dreams.

The differences in the frequency of sexual dream reports between the higher percentage in European reports and the lower percentage in reports from American studies may well be methodological; the former were reporting percentages from actual dream reports while the latter were of recall of an experienced dream type. The Finnish study of frequency within a group of dreams reports of 8% with sexual content is much like the American studies in methodology and has similar results. Older individuals report sexual experiences in dreams; interestingly a change in frequency of sexual experiences with age is not clearly demonstrated in these studies.

Affect

The assumption has been that all dreams must contain affect, as affect is considered the force that drives the dream narrative. Kramer and Glucksman [52] found affect in 58% of the first and last dreams reported in treatment by analytic patients. Kramer *et al.* [43] reported that 80% of the dream reports of a representative sample of adults' dreams contained affect while Hall and Van De Castle [6] found affect in 70% of their college-aged sample norms. In laboratory-collected dreams, affect was found in 12.5% by McCarley and Hobson [53], 35% by Snyder [54], and 40% by Kramer and Brick [55]. When probed about affect [56], 70% of reports contained affect and when laboratory subjects rated their own dreams 72% had affect [57]. Merritt *et al.* [58] using a vigorous probe technique on home dreams showed a 10-fold increase in the amount of dream affect. Fosse *et al.* [59] found affect in 74% of home self-awakenings from REM sleep using a probe technique in eliciting affect. Home dream reports of college students who rated their own dreams [60] reported affect in 93% of them and 86% of dream reports of elderly women [61] contained affect. Barad *et al.* [17] found that elderly residents in a home for the aged had dreams of "lost resources," themes which were similar to those found in a group of elderly subjects living independently [18]. They noted that the dream of "lost resources" may reflect the beginning of a chronic brain syndrome, and that mentally intact elderly subjects, about half of their group, had dreams that were actively goal directed, richly varied, and elaborate.

Home dream reports may not be representative of all dreaming and probing for affect in dreams may create a demand situation in which the subject feels he or she must find some emotional content, as affect does not appear to be universally present in dreams as noted by Strauch and Meier [57]. Foulkes [62] has raised an alternative hypothesis that dreams are narratively driven and emotion is simply congruent with the plot. Kramer and Glucksman [52] found that if associations to the dreams were included, 98% of the dream reports of analytic patients had an associated affect.

Both of the Hall and Van De Castle [6] and the Kramer *et al.* [43] studies found that unpleasant dream tone was more frequent than pleasant, 57%/14% in the former and 12%/4% in the latter, with neutral being a very common tone (29% in Hall and Van De Castle [6] and 75% in the Kramer *et al.* [43] study). The word length in the former study is six times as long as in the latter and may account for the frequency difference. The finding that dream reports have a predominantly negative tone in self-reported dreams was found in 80% of college-aged subjects' dreams [6] and 54% of the adult sample of dreams reported by Kramer *et al.* [43].

Merritt *et al.* [58] found that anxiety was the commonest emotion with joy-elation second. The same predominance of negatively toned dream reports was true for laboratory-collected dreams: 52% by Strauch and Meier [57], 67% by Snyder [54], and 70% by Foulkes *et al.* [56]. However Fosse *et al.* [59] found a balance in negative and positive emotions, as did Schredl and Doll [63]. Kramer and Glucksman [52] found that a shift in the predominant valence of the dream report from negative (77%) to positive (53%) occurred in comparing the first to the last dream report in long-term analytical therapy perhaps reflecting improvement in therapy.

St-Onge *et al.* [64] in the introduction to their article state, "… age has an influence on the frequency and valence of dream emotions." They found that the home dreams of older women had fewer negative emotions and were of lower intensity than those of younger women. The results from a number of cross-sectional studies [27, 40, 61, 65, 66, 67] of women ranging in age from the second to the seventh to eighth decade point out that the frequency of emotions, particularly negative ones, decreases with age. Comparable studies with men have not been done [61].

Brenneis [40] observes that the expression of emotion, positive or negative, decreases as the woman

grows older. Cote *et al.* [66] also found a decrease in the frequency of emotion with age and fewer negative outcomes. However, the activity level, autonomy, and achievement striving of the dreamers increased with age from the 20s to the 50s. Zanasi *et al.* [41] found that the young and the old have different ways of dreaming. The young use more words in describing emotions. Older people when expressing emotion shift between past and present more often than younger people.

Winget *et al.* [7] found women were more likely to report a dream and that those over 65 had the highest frequency of death themes and that guilt in dreams was low in general but highest in the youngest age group (21–34). Howe and Blick [61] found that the elderly subjects reported two emotions per dream. The most frequent emotion in the diary-reported dreams of these elderly women was enjoyment, which occurred in 19% of the reports followed by surprise in 15% and distress in 14% with confusion or frustration in another 14%. Blick and Howe [65] in a follow-up study comparing the diary-collected dreams of young and elderly women reported that the younger women had more emotions in their dreams (2–4), compared to elderly women (1–3). Enjoyment was a greater proportion (19% vs. 10%) of the emotions in the dreams of the elderly women and anger (4% vs. 10%) and fear (11% vs. 17%) occurred less often than in the dream reports of younger women.

Lortie-Lussier *et al.* [67] found a striking consistency across dream reports from a group whose mean age initially was 29 and at a second dream collection was 44. They found change in only 2 of 12 comparisons, namely decreases in aggressive and friendly interactions. The study was not of the elderly, but shows remarkable content consistency across time and that content changes reported in the elderly may have occurred much earlier and just continued in the dreams of the elderly as Waterman [27] has noted, large reductions occurred in aggression, friendliness, and emotion before age 45.

The impression that the literature review on affect in the dreams of the elderly leads to is that in the elderly, as in the young, affect is not an inevitable accompaniment of dreaming, even when it is vigorously pursued with various probes and rating stances, such as self-rating rather than rating by others. Affect in dreams tends to be negative. Affect in dream reports decrease with the age of the dreamer and become less negative and less intense. Death themes are greater in the older person's dreams.

Regression

Smith and Hall [42] offer the results of an exploration from the dreams of a single person, the senior author, as a test of the hypothesis that as the age of the dreamer increases she or he will dream more of the past. They examined 649 dream reports experienced by the dreamer between the ages of 25 and 76. A dream was rated as having regressive content if the content referred to a time at least 1 year before the dream. Some 27% of her dreams had regressive content but regressive content did not increase as the dreamer grew older. Nor did regressions go further back in time as she aged. The proportion of dreams with an oral reference, food or eating, or a reference to her mother, or to toilet activities, or to losing or forgetting things remained essentially the same over the 50 years of dream collection. Lortie-Lussier *et al.* [67] found a similar consistency in a group of 21 women across 10–17 years. The stability of references to the past in these dreams [42] argues for the content of dreams being remarkably consistent across time in contrast to the changes that have been described earlier in this report. The fact that in the Smith and Hall study [42] the dreams reported are those of a single individual significantly limits the generalizability of the results, but it gives one pause about concluding that dream content change is an inevitable accompaniment of aging; it may depend on what content is being assessed.

Nathan *et al.* [34] investigated the relationship between brain atrophy (as measured by computerized transaxial tomography [CTT] scans) and types of dreams (one of which was labeled by them as "regressive") in 170 elderly subjects with a mean age of 73. They found that patients with minimal atrophy showed large numbers of "regressive" dreams in contrast to those with moderate to severe atrophy that have a preponderance of "lost resources" dreams. Unfortunately, no definition of a "regressive" dream is included, nor is the frequency of this dream type in younger individuals provided for comparison to establish it is a dream type that is more common in the elderly. We are left with the authors' statement that the regressive dream is more common in those with minimal brain atrophy. Without definition, quantification, or comparison, the observation of "regression" remains regrettably unsubstantiated.

Grenier *et al.* [26] explored whether the time references in dreams, home and laboratory, and autobiographical memory in 28 young (18–25) and 30 older

(60–77) women followed the same pattern. The investigators analyzed home and laboratory reports as well. They found that for dreams and autobiographical memory in young adults there was a high frequency of recent temporal references that decreased with increasing remoteness (a retention function component) ending with a paucity of temporal references to childhood (a childhood amnesia component). For older adults, they found a high frequency of temporal references dating back 10–20 years, decreasing in frequency with increasing remoteness until about 30 years ago (a retention function component). There followed a resurgence of temporal references to experiences originally occurring in adolescence and/or young adulthood (a reminiscence component). Lastly, there was a paucity of temporal references to experiences in early childhood (childhood amnesia component). However, there were more childhood memories identified in the older group than the younger group. The so-called "bump" in temporal references to adolescence/young adulthood in the older age group and their having more temporal references to childhood suggests that "regression" does occur in the dreams of the elderly as well as in their autobiographical memory. Greiner and her colleagues [26] speculated that the temporal reference bump to adolescence/young adulthood has to do with reconstituting one's identity in later life using memories from the earlier period that is so involved with identity formation. This study supports the view that there is regression in dreams and waking life in the elderly.

Schredl and Piel [68] point out that events of high salience, such as experiencing a war, may continue to appear in dreams at a high rate even 50 years later. This may fit a regression model, as the high salience event doesn't appear in all dreams. The war may be like the adolescent/young adult "bump" described by Greiner *et al.* [26].

The high consistency across time of dream contents and the content deviance from the Hall and Van De Castle norms [6] suggest that regularity rather than regression occurs in most content categories [64, 67].

It appears that "regression" does occur in dreams as it does in waking memory and the high salience of an event may explain its reappearance in dreams.

Dreaming style

In a study of Navajo men, Krohn and Guttmann [39] noted a shift in their dreams from an active productive orientation in younger men (ages 35–54), to a receptive, accommodating, and magical orientation in the dreams of older men (ages 55–95). The investigators interviewed 70 Navajo men and collected a dream report from each subject and found that non-work references were highest in their older age group, and that self representation of the dreamer as active and as the central figure in the dream was greatest in their younger age group, while their older age group was most likely to see the dream experience as having consequences in reality. The older age group had the dream setting more often as outdoors and that the locus of control was seen by the older group as more often with the dreamer while the younger saw the dream experience as out of their control. The older dreamer sees himself as passive and not the central figure in the dream that is linked to waking reality.

Brenneis [40] compared the dreams of women aged 40–85 to those of women aged 16–17 and 18–26. In a detailed and thoughtful analysis the investigators found that the dreams of the youngest age group were banal, diffuse and vague, those of the young adult women were longer, detailed, elaborate and graphic, and the older women's dreams were detailed and quiet. The older women dreamed in a more restricted dream space, had the fewest characters, and the highest ratio of relatives and strangers. Compared to the other two groups the older women had a greater degree of activity and a decreased sense of being the central figure in the dream but with a theme of running out of resources. The older women showed a decrease in aggressive but not of sexual interactions. They also had a perceived reduction in the ability to give or get nurturance, with food being a case in point. The internal narrowing of "internal personal investments" was associated with an active sense of self. The older women's dreams in summary showed a "narrowing of internal personal investments, a decrease in concerns about aggression, a decrease in the dreamer's sense of herself as pivotal and… an augmented amount of internally represented robust and locomotor activity." The contrast with the passivity reported in the dreams of older Navaho men [39] is noteworthy.

Weisz [69] reported on the content of laboratory-collected dreams of four elderly men, aged 60–71, who slept for four non-consecutive nights. He noted the passive participation of the dreamer in the dream, a decreased impulse expression with low ratings of sexuality and aggression, and more recreational and social themes and very clear temporal regressions. Interesting, but too small a sample (31 dreams) to

build on except to see the passivity as similar to the dreams of elderly Navaho men [39] and the presence of temporal regression.

Barad *et al.* [17] reported that in sexual dreams elderly men felt anxiety and failure, but women reflected passive, pleasurable gratification of dependency needs in theirs. Altshuler *et al.* [18] found that the elderly leading active lives were also active in their dreams. Fein *et al.* [31] found that the number of action words and visual nouns were reduced in the dreams of elderly women. Zanasi *et al.* [41] also noted a decrease in visual references in the dreams of their elderly subjects.

These studies thus suggest that gender is a factor that modulates the effect of aging on dream content. With advancing age the dreams of healthy elderly women may get more active and more narrowly focused while those of elderly men may get more passive. The activity level differences in the dreams of the elderly may reflect waking life differences for elderly men and women. The dreamer is less likely to be the central character in the dream. The decline in visual references may have both psychological and physical explanations.

Dreaming disorders

The three major disorders of dreaming include nightmares, defined as frightening dreams often associated with awakening, Charcot-Wilbrand syndrome, in which dreaming is lost following focal damage to the brain, and REM behavior disorder, in which the inhibition of motor activity is lost and the dreamer acts out his dreams.

Nightmares

In a study of the prevalence of nightmares in the healthy elderly, Salvio *et al.* [70] collected both retrospective estimates of nightmare frequency and two-week dream logs from 51 healthy elderly subjects (36 women and 15 men) with a mean age of 65. Nightmares were defined as frightening dreams without apparently any comment on whether one awakened or not. The comparison group was 220 college students, mean age 19, who provided information about nightmares as part of a class exercise.

The elderly subjects provided fewer nightmares and had fewer problems with nightmares than the comparison group of college students. Retrospective reports significantly underestimated the frequency of the nightmare experience, by a factor of 10 for the elderly and of two and a half for the college students. Almost twice as many students (46%) as elderly (25.5%) reported at least one nightmare while keeping the two-week nightmare log. Four and a half times as many students (19.5%) as elderly (4.3%) reported having trouble with nightmares. It is the people who are troubled by nightmares who are likely to seek help [71]. Funkhouser *et al.* [25] speculated that the decrease in nightmares in the elderly may reflect a decreased interest in nightmares on the part of the elderly, as they are generally less interested in dreams [22, 24].

Charcot-Wilbrand syndrome

Charcot originally described the syndrome in 1883 in a patient who was unable to recall the images in his dreams. Wilbrand in 1887 reported a case of cessation of dreaming after occipital-temporal infarction. The label Charcot-Wilbrand syndrome [72] is now applied to patients with dream cessation following a focal lesion. These individuals have an associated failure to revisualize during wakefulness (visual irreminiscence), the inability to recognize familiar faces (prosopagnosia), and are disoriented in familiar places (topographagnosia).

Solms [72] reported on an extensive series of 361 of these patients studied neuropsychologically to specify their functional deficits and with brain scans to confirm lesion sites. The average age of the patients in his series was 36; nevertheless it is a condition that occurs in the elderly and offers important insights into the biology of dreaming. The loss of dreaming occurred in patients who had either: (1) a bilateral medio-basal frontal cortex lesion involving fibers from the ventral tegmental area of Tsai, an appetitive center that is the source of seeking wishing/desiring behavior; or (2) a lesion of the inferior parietal area of either side of the brain, which on the right involves spatial orientation and on the left involves symbolic activity. If the parieto-tempero-occipital area is involved, the ability to have visual elements in dreaming is lost as well the ability to create images awake. Interestingly, from a psychoanalytic point of view [73], individuals who reported the loss of dreaming also reported poor sleep.

Dreaming according to Solms [72, 74] is initiated by any arousing stimulus, e.g. REM sleep, noise, or a seizure. This stimulus activates the ventral tegmental area of Tsai, a dopaminergic system, whose circuits are connected to frontal and limbic structures that instigate goal-seeking behavior. This goal-seeking

behavior is blocked by anterior limbic structures, so acting out the dream does not occur, and a backward projection is initiated. The dorso-lateral and occipital areas are inhibited. The inferior parietal cortices are activated providing the spatial (right side) and symbolic (left side) aspects of dreaming. Lastly the occipital associative areas provide memories out of which the dream is actively constructed.

A major critique of the conclusions of Solms [75] is whether the determination that the subjects studied were not dreaming was based on awakenings from REM sleep, which they were not. Bischof and Bassetti [76] report a case of Charcot-Wilbrand in a 73-year-old woman that had bilateral occipital artery infarction with infarction deep in the occipital lobes, lingual gyrus, and right postero-lateral thalamus. The patient had repeated polysomnography and demonstrated an essentially normal sleep architecture. Repeated REM sleep awakenings were done on one night without the patient reporting any dream experience. The patient could imagine familiar surroundings, was able to recognize familiar faces, and was spatially oriented, which raises questions about the diagnosis.

REM behavior disorder

REM behavior disorder (RBD) is a parasomnia first described by Schenck *et al.* [77] in which patients act out their dreams, often in a destructive manner because of a loss of the motor inhibition that usually accompanies REM sleep. Fantini *et al.* [78], in a review article, point out that RBD usually occurs in older men and its prevalence is about 0.5%. The condition may be idiopathic in 60% of cases but an association with the alpha-synucleinopathies has been described. RBD may be the beginning of a neurodegenerative disease such as Parkinson's, dementia with Lewy bodies, and multiple system atrophy [79]. Turner [80] suggests that RBD may be the result of neuronal loss in the locus coeruleus and substantia nigra.

To explore the possibility that patients with RBD have an aggressive personality that is reflected in their dreams, Fantini *et al.* [81] studied a group of 41 patients with polysomnographically demonstrated RBD and an average age of 68 and found they had a higher percentage of dreams with aggression on a dream questionnaire compared to a control group (66% vs. 15%). Importantly waking levels of aggression did not differ between the groups. Parkinson's patients with clinically diagnosed RBD had more violent dreams than those who did not have RBD [82].

The three disturbances of dreaming have potentially diagnostic significance. Nightmares that are associated with discomfort may indicate an increase in stress in the life of the dreamer. The sudden onset of a loss of dream recall may indicate the presence of an isolated brain lesion. And, the development of a RBD may be the initial symptom of a degenerative disease.

Conclusion

Dream recall decreases with the age of the dreamer in both home and laboratory dreams in both men and women. As the dreamer ages, characters in the dream decrease, the dreamer is less likely to be the center of the dream action, and there are more family characters in the dream report.

Social interactions in dreams are more commonly aggressive then friendly and least common are sexual interactions. Aggressive social interactions decrease as the dreamer grows older, while other aspects of the aggressive interactions such as witnessing, victimhood, and the effect of the sex of the dreamer all change with the age of the dreamer. There is the suggestion that friendly interactions decrease with the dreamer becoming older and there may be differences between the sexes as well. A change in the frequency of sexual dreams with aging is not clearly demonstrated perhaps because of the relatively low frequency of such reports.

Affect is not an inevitable aspect of the dream report. When present, affect tends to be negative. Older dreamers report fewer dreams with affective content and those which do have this content are less negative and less intense than those of younger dreamers. Death anxiety is more common in older subjects.

Regression in time occurs in dreams as it does in waking memory, influenced by the salience of the historical event and its relevance for the dreamer's current preoccupations.

The style of dreaming changes with the age of the dreamer with men getting more passive in their dreams while women appear to get more active. Visual references decline with age.

Disorders of dreaming and specific dream contents, like dreams of lost resources, may well have diagnostic significance.

The cross-sectional nature of the studies of dreaming in older people limits their usefulness in developing an unfolding understanding of the effect of aging on their dreams. Nevertheless there do appear to be important changes in dreaming associated with

being older. The view [83] that "… age is not a major factor in shaping dream content once Americans have reached young adulthood" is not tenable.

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Part 3
Chapter
30

Sleep disorders in the elderly

Sleep medication and traffic safety in the elderly

Monique A. J. Mets and Joris C. Verster

Introduction

It has been estimated that in 2020 more than 15% of drivers will be over 65 years old [1]. Driving a car is an important way for the elderly to maintain their independence, since other forms of transportation such as walking or riding a bicycle may become compromised during aging. Consequently, most elderly people do not want to stop driving. Moreover, patients (and healthy people) often regard driving a car as a right and not a privilege [2]. It has been shown that driving cessation has been associated with increases in reports of depressive symptoms [3]. On the other hand, driving performance may become less efficient with advancing age and traffic accident risks may increase accordingly. With advancing age there are well-documented declines in cognitive functioning, motor ability, and reaction time that are only partly compensated for by increased driving experience (when compared to younger drivers) [4]. In addition, peripheral vision worsens with increasing age [5]. Taking both the issues of mobility and safety into account, accurate assessment of driving ability is of great importance. Driving a car is an example of complex behavior that requires concurrent use of cognitive, perceptual, and motor skills. Although driving is practiced often and parts of driving become more or less automatic processes (e.g. using the gear) several other skills and abilities used during driving require active attention and concentration (e.g. anticipating the behavior of other drivers). In fact, the majority of traffic accidents are caused by driver inattention.

This inattention may be caused by insomnia or by (residual) effects of sleep medication. Insomnia, which is common among the elderly, is often treated with hypnotic drugs. In fact, when compared to young adults, elderly patients account for a much larger number of prescriptions for sleep medications [6, 7, 8, 9, 10, 11]. Although elderly patients greater than 60 years of age represent only 22% of western European populations, they receive 54% of all prescribed drugs [12]. Approximately 9% of the elderly use benzodiazepines. With increasing age these percentages increase rapidly [13, 14]; one survey confirmed that the absolute percentages of traffic accidents among the elderly increased by 43% from 1980 to 1989. In contrast, the increase for the population as a whole equaled only 8.9% [15]. Adjustments for total miles driven and yearly mileage (driving exposure) confirm that the elderly have more accidents for the number of miles driven [16]. This chapter gives a concise overview of the impact of the use of sleep medication on traffic safety in the elderly.

On-the-road driving tests

Various benzodiazepine hypnotics have been tested in healthy subjects using the on-the-road driving test [17]. On-the-road tests have not been performed in the elderly yet. However, findings of driving impairment in healthy young adults are likely to be of greater magnitude in the elderly.

The on-the-road test uses an instrumented car, designed to measure the speed and position of the car objectively within the right traffic lane (Figure 30.1). A camera mounted on the roof of the car continuously measures the car's position relative to the lane delineation. This data is used to calculate the weaving of the car, i.e. the standard deviation of lateral position (SDLP). SDLP is the primary outcome measure of the driving test. With reduced vehicle control, weaving (and thus the SDLP values) increases (Figure 30.2).

Several studies have examined the residual effects of benzodiazepine hypnotics on driving ability. In the studies hypnotic drugs were taken for 1 or 2 nights at bedtime. The driving tests were performed the following morning (10–11 hours after intake) and in the afternoon (16–17 hours after intake), corresponding to the times one drives to and from work. Car weaving performance following the use of benzodiazepine hypnotics, and as measured by SDLP increments, is compared to performance after placebo use, and is shown in Figure 30.3.

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Figure 30.1. The instrumented car. Note that the camera for lateral position measurements is equipped with two infrared lights, to enable recording during the night and dark weather circumstances.

Figure 30.3 shows that benzodiazepine hypnotics significantly impair driving performance. Driving impairment was most pronounced in the morning. In the afternoon, driving impairment was less evident and absent for short-acting benzodiazepines. However, for long-acting benzodiazepines, and especially when administrating higher dosages than recommended, driving was also impaired in the afternoon.

To illustrate the magnitude of driving impairment, effects of different dosages of alcohol [18] are also depicted in Figure 30.3. These alcohol concentrations correspond to the most common legal limits for participating in traffic. For example, in The Netherlands driving is not allowed for experienced drivers who have blood alcohol concentrations of 0.05% and above, or for novice drivers (i.e. those who are within the first 5 years after obtaining their driver's license) with concentrations of 0.02% and above. It is evident from Figure 30.3 that driving impairment after intake of most benzodiazepine hypnotics is worse than what is regarded as acceptable for alcohol.

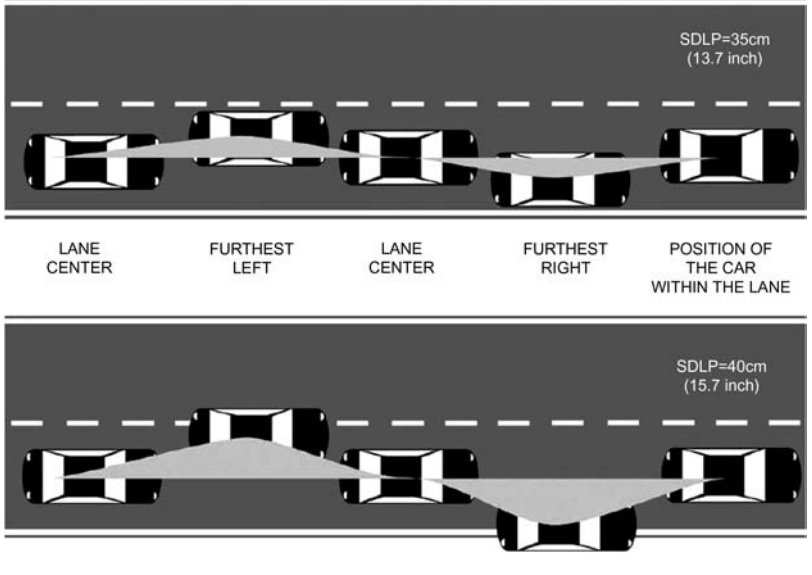

Figure 30.2. Standard deviation of the lateral position (SDLP).

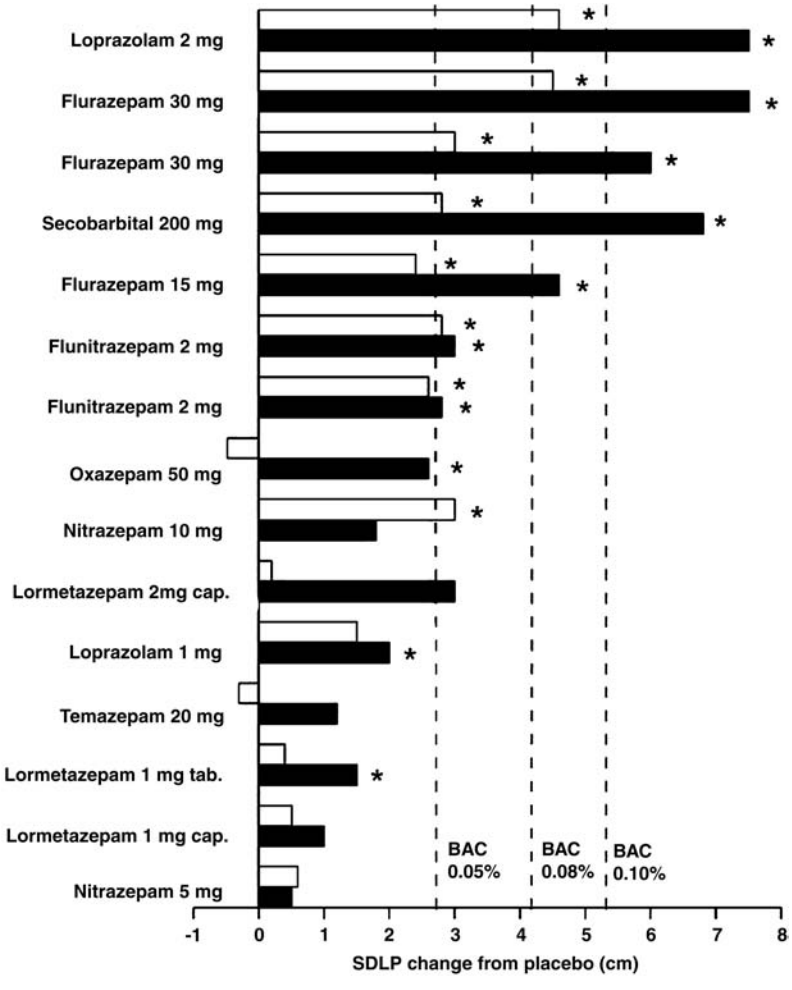

Figure 30.3. Benzodiazepine hypnotics and driving performance. Standard deviation of lateral position (SDLP) increments relative to placebo are shown. Driving tests were performed in the morning (white bars) and afternoon (black bars) (10–11 and 16–17 hours after bedtime administration, respectively). Significant differences from placebo are indicated by an asterisk; dotted lines indicate levels of SDLP increment observed with most common legal blood alcohol limits for driving a car. Adapted from [15] with permission from Elsevier.

A meta-analysis [19] confirms that both a single dose (effect size (ES) = 0.42; 95% confidence interval (CI) = 0.14 to 0.71) and double dose (ES = 0.68; CI = 0.39 to 0.97) of benzodiazepine hypnotics significantly impair next-morning driving performance. In the afternoon, 16–17 hours after intake, driving is still significantly impaired when twice the recommended dose is administered at bedtime (ES = 0.57; CI = 0.26 to 0.88).

The Z-drugs zopiclone, zolpidem, and zaleplon were developed to overcome the unwanted residual effects of benzodiazepine hypnotics. Unfortunately, the introduction of zopiclone was not associated with improvements in driving performance. Several on-the-road studies showed pronounced driving impairment after intake of zopiclone. SDLP increments ranged between 3 and 8cm, comparable to impairment observed for blood alcohol concentrations above 0.05% (the legal limit for driving in many countries). Epidemiological evidence revealed that those who use zopiclone have a four-fold increased risk of having a traffic accident [20].

Zolpidem when taken as recommended has no residual effects on driving ability and thus is a great improvement when compared to benzodiazepines and zopiclone. However, dose-dependent impairment is evident when shortening the time between intake and driving [21]. Also of concern are the findings of a recent study that reported a substantial number of cases of zolpidem misuse and abuse [22]. During the daytime, drivers who had taken higher dosages than recommended were stopped for impaired driving or involvement in accidents. These accidents included collisions with stationary objects and driving on the wrong side of the road. One third of these drivers on zolpidem were often unaware of driving at the time they were stopped and after the incident had no recall of how they ended up driving their car.

Zaleplon had no negative residual effects on driving ability. Even when taken in the middle of the night (i.e. 4 hours before driving), twice the recommended dose of zaleplon did not affect driving performance [21]. No epidemiological data on traffic accident risk is available yet for zolpidem and zaleplon.

Epidemiological evidence

Several epidemiological studies examined the traffic accident risk in elderly drivers treated with psychoactive drugs. Ray and colleagues [23] showed that the use of benzodiazepine drugs (diazepam, lorazepam, chlordiapoxide, and clorazepate) significantly increased traffic accident risk (OR = 1.5; 95% CI = 1.2 to 1.9). Higher dosages elevated traffic accident risk (OR = 2.4; 95% CI = 1.3 to 4.4), as well as using more than one benzodiazepine drug (OR = 4.8; 95% CI = 1.6 to 14.5). In another study of the effects of benzodiazepines on driving performance, Neutel [24] examined the odds ratio of being involved in a serious traffic accident (and whether the injuries required hospitalization) of over 78 000 benzodiazepine users (triazolam or flurazepam) when compared with those of 97 862 healthy non-users of the drugs. Figure 30.4 shows the risk of requiring hospitalization following a traffic accident among those being treated with a benzodiazepine hypnotic. Patients were followed-up to 8 weeks after treatment initiation.

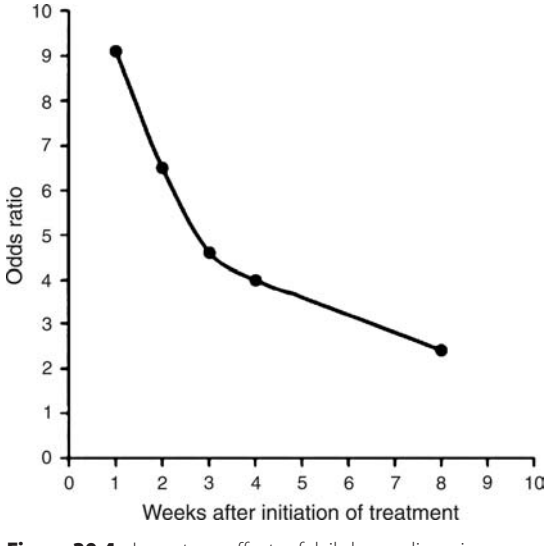

Figure 30.4. Long-term effects of daily benzodiazepine use on traffic safety. The data in the figure, which are taken from the Saskatchewan Health Database, show the odds ratios of the association between continuing benzodiazepine use and the risk of becoming hospitalized following a traffic accident injury. The records of 78 070 patients using a benzodiazepine hypnotic (triazolam or flurazepam) were compared to those of 97 862 healthy control subjects. Note that the risk is highest after treatment initiation and then gradually decreases. Adapted from [15] with permission from Elsevier.

Overall, risk of traffic accident injury for patients using benzodiazepine hypnotics was 3.9 times higher than that for the healthy control subjects. It is evident from Figure 30.4 that after treatment initiation traffic accident risk gradually decreases. Nevertheless, after 8 weeks traffic accident risk is still more than twice the magnitude of that of healthy controls. Hemmelgarn and colleagues [25] examined the risk of traffic accident involvement in elderly benzodiazepine users. Patients were followed-up to 1 year after treatment initiation. Elderly patients who used benzodiazepines with a long half-life had a significantly increased risk of having an accident after 1 week (OR = 1.45; 95% CI = 1.04 to 2.03) and 1 year (OR = 1.26; 95% CI = 1.09 to 1.45) after treatment initiation. In contrast, for benzodiazepines with a shorter half-life the relative risks were not significant.

Although these findings show that elderly patients who use benzodiazepine hypnotics are at increased risk of having an accident, other studies did not [26, 27].

Discussion

Patients who suffer from insomnia often depend on sleep medication to get a good night's rest. This chapter shows that in terms of traffic safety there are important differences in safety of hypnotic drugs. Benzodiazepines produce significant impairment during the morning following bedtime administration. This impairment is more pronounced with higher dosages and with hypnotics having a long half-life. When time between administration and driving is shortened, impairment also becomes more pronounced. Nevertheless, some benzodiazepine hypnotics also produced impaired driving in the afternoon, i.e. 16–17 hours after intake. For these drugs and dosages driving seems unsafe all day. Zopiclone showed no improvement relative to the benzodiazepine hypnotics: several on-the-road studies showed significantly impaired driving. Zolpidem and zaleplon, when taken as recommended, did not affect driving performance.

It is evident that the elderly may be more vulnerable to the adverse effects of sleep medications. Also, renal and hepatic function decreases with aging. As a result elderly patients are exposed to higher blood drug concentrations. In addition, the half-life of drugs increases causing drugs to remain present in the blood

for a longer time when compared to young adults. Therefore, elderly patients often receive half the adult dosage, i.e. 3.75mg zopiclone instead of 7.5mg. It should be noted that none of the driving studies discussed in this chapter were performed in the elderly. In fact, all studies used healthy adults without insomnia. Therefore, results from the driving studies in adults may not be entirely representative of the geriatric population. However, the findings are in line with epidemiological data of older drivers showing increased traffic accident risks. Also, the results are supported by studies in elderly patients who showed significant impairment on cognitive and psychomotor tests. Nevertheless, further driving studies should be performed in elderly subjects using the adjusted dose. Preferably, driving studies should also examine the effects of long-term treatment, because the currently available studies solely measured acute effects after 1–2 nights of treatment. Epidemiological studies show that tolerance develops slowly and that even after 1 year of treatment accident risks of benzodiazepine users are still elevated relative to healthy controls.

Studies in elderly patients will have to be set up carefully. Figure 30.5 shows that several factors play a role and will affect the outcome of such a study.

As age increases, driving performance worsens. Furthermore, insomnia may have a negative effect on driving. On the other hand, sleep medications may reduce the impact of insomnia on driving performance, but at the same time may produce side effects that affect driving. Over time, insomnia may be relieved and partial tolerance may develop to the side effects of sleep medication. Given the fact that insomnia is common among the elderly, future studies should take the factors above into account. The pharmaceutical industry should aim at developing sleep medications that do not act via the GABA system in their effort to improve the side-effect profile of this class of drugs.

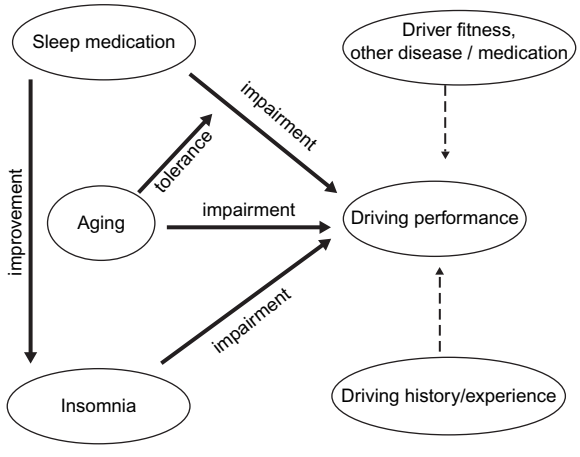

Figure 30.5. The complex interplay among factors that affect or improve driving performance in elderly drivers.

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Part 4 Treatment of sleep disorders in the elderly

Part 4
Chapter
31

Treatment of sleep disorders in the elderly

Geriatric psychopharmacology: an overview

Andrew D. Krystal

Introduction

The subject of the pharmacological treatment of insomnia is of particular relevance to older adults as the frequency and duration of the pharmacological treatment of insomnia increases with age [1, 2, 3, 4]. This article is intended to provide a general introduction to the process of medical decision-making regarding insomnia medications in older adults. While this process is in principle the same as in younger individuals, it is complicated in the elderly by the potential for more serious consequences of insomnia, the relative absence of available data from placebo-controlled trials upon which to base decisions, and the greater risks of adverse effects. This discussion is meant to serve as a framework for thinking about the pharmacotherapy of insomnia in older adults, which will be discussed in more detail in the subsequent chapters.

Treatment decision-making in older adults

While chronic insomnia is generally associated with significant morbidity, including sleep disturbance, reduced qualify of life, and reported daytime impairment, it may have particularly serious consequences among older adults. Older adults may be at increased risk for falls/hip fractures, cognitive impairment, nursing home placement, and perhaps even early mortality [5, 6, 7, 8, 9]. These adverse consequences would appear to provide a strong impetus for considering implementing pharmacotherapy for elderly individuals with insomnia in clinical practice. Which of these consequences should be used in treatment decisions, however, depends upon which are mitigated by therapy. This is based on the logic that the decision of whether to implement treatment should reflect a determination of whether there is evidence that treatment provides benefits by mitigating the adverse effects of insomnia that are not outweighed by the adverse effects of the therapy [10]. As a result, more severe impairment or greater risks for impairment in an individual should lead to greater motivation to implement treatment. At the same time, greater risks for adverse effects should result in greater hesitancy to administer therapy. In this regard, there is good reason to believe that older individuals are more likely to experience adverse effects and may experience more severe consequences of such effects when they occur [11, 12, 13, 14]. These considerations illustrate the complexity of treatment decision-making in the elderly relative to younger adults; there is both greater motivation to treat and more reason for caution about the adverse consequences of treatment. In the subsequent sections we provide a general discussion of the evidence for benefit and the risks of adverse effects related to making clinical decisions regarding the pharmacological treatment of insomnia in older adults.

The available data on the therapeutic effects of insomnia medications in the elderly

A number of different classes of medications are used to treat insomnia in older adults (Table 31.1). These include the benzodiazepines (including triazolam, temazepam, flurazepam), agents referred to as "non-benzodiazepines" (including zolpidem, zaleplon, eszopiclone, zopiclone, and indiplon), which have a mechanism of action related to the benzodiazepines but an unrelated chemical structure, antidepressants (including trazodone, amitriptyline, doxepine, and mirtazapine), antipsychotics (including quetiapine, olanzapine, and risperidone), the melatonin receptor agonist ramelteon, and a wide range of over-the-counter medications that are primarily H1 antagonist antihistamines.

Considering the frequent use of these medications in older adults, there is a surprising lack of data on their efficacy and safety in this population [1, 2, 3, 4].

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Published by Cambridge University Press.

Table 31.1. Medications used to treat insomnia in the elderly

Agent	Medication type	Usual dosage in elderly	FDA approved indication	Evidence of efficacy in older adults?
Triazolam	Benzodiazepine	0.125–0.25 mg	Insomnia	Yes
Temazepam	Benzodiazepine	7.5–30 mg	Insomnia	Yes
Flurazepam	Benzodiazepine	15–30 mg	Insomnia	Yes
Zolpidem	Non-benzodiazepine	5 mg	Insomnia	Yes
Zaleplon	Non-benzodiazepine	10 mg	Insomnia	Yes
Eszopiclone	Non-benzodiazepine	2 mg	Insomnia	Yes
Trazodone	Antidepressant	25–100 mg	Depression	No studies
Amitriptyline	Antidepressant	10–50 mg	Depression	No studies
Doxepine	Antidepressant	10–50 mg	Depression	No studies
Mirtazapine	Antidepressant	7.5–30 mg	Depression	No studies
Quetiapine	Atypical antipsychotic	25–100 mg	Schizophrenia/mania	No studies
Olanzapine	Atypical antipsychotic	2.5–5.0 mg	Schizophrenia/mania	No studies
Diphenhydramine	Antihistamine	25 mg	OTC allergy/insomnia	No studies
Doxylamine	Antihistamine	25 mg	OTC allergy/insomnia	No studies

To date, 12 placebo-controlled trials of the pharmacological treatment of insomnia have been carried out in older adults [10]. Of these, five have employed polysomnographic outcome assessment [10]. Seven agents have been demonstrated to have efficacy in improving either sleep onset or sleep maintenance difficulties or both including benzodiazepines (triazolam, flurazepam, and temazepam), non-benzodiazepines (zolpidem, zaleplon, and eszopiclone), and the melatonin receptor agonist ramelteon [10]. Of these studies only two reported improvement in any measure other than sleep [15, 16]. In these studies there was evidence that treatment with eszopiclone led to improvement in morning sleepiness, and a decrease in number and duration of naps in those who napped. In one of these studies, active treatment had a significant advantage over placebo in improving the physical functioning and vitality subscales of the SF-36, while in the other there was a treatment effect on self-ratings of "daytime alertness." Whether other agents might have had effects on daytime functional outcomes remains unknown as these data were generally not reported in other studies [17]. Overall, these studies provide a relatively meager foundation for carrying out empirically based risk–benefit assessment. They suggest that along with sleep disturbance, measures of daytime sleepiness, vitality, and alertness have been noted to improve with at least some treatments, and should provide motivation for considering implementing pharmacotherapy for elderly individuals with insomnia in clinical practice.

Notable areas where data are lacking include long-term treatment and insomnia occurring co-morbidly with medical and psychiatric conditions. Despite the fact that the duration of pharmacological therapy increases with age, the duration of the longest placebo-controlled trial in older adults is substantially shorter than the longest trials carried out in younger adults [1, 4, 18, 19]. The longest such study in the elderly is 8 weeks in duration, whereas in younger adults two 6-month placebo-controlled trials have been carried out [18, 19, 20].

The difference in available data between older and younger adults is even greater for insomnia occurring co-morbidly with medical and psychiatric disorders. While trials have been carried out with insomnia occurring with major depression, generalized anxiety disorder, rheumatoid arthritis, chronic obstructive pulmonary disease, and alcoholism in younger adults, there has yet to be a trial of the treatment of co-morbid insomnia in the elderly [21, 22, 23, 24, 25, 26, 27].

Another important gap in the knowledge base is data on the efficacy of some of the most commonly prescribed insomnia agents. This includes trazodone, amitriptyline, mirtazapine, and quetiapine [28].

Risks of pharmacotherapy in older adults

There are a number of factors that increase the risks of adverse effects in older insomnia patients including: (1) slower medication elimination leading to increased serum concentrations of the drug, which in turn increases the risk for side effects and the duration of effects; (2) a higher likelihood of pre-existing cognitive impairment; (3) a predisposition to developing cognitive impairment; (4) vulnerability to experiencing fractures due to falling; (5) greater likelihood of concurrent medications that could interact with an insomnia agent; and (6) greater likelihood of having a medical disorder [11, 12, 13, 14].

Of these vulnerabilities, the data on the risk of falls is the most complicated. Falls clearly represent a significant cause of morbidity and mortality in the elderly with death occurring within 6 months of 25% of such events [9, 29, 30]. The complication arises because of evidence that insomnia increases the risk of falls, while at the same time benzodiazepines, non-benzodiazepines, and agents with anti-cholinergic and anti-adrenergic effects have the potential to predispose individuals to falls [9, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41]. Of note, the studies which have documented an association of a greater likelihood of falls with these medications generally did not account for the risk of falls due to insomnia [34, 35, 36, 37, 38, 39, 40, 41]. While there is reason to believe that both insomnia and some insomnia medications might increase the risks for falls, we currently lack means to determine in which individuals treatment of insomnia might be indicated based on falls risk.

In addition, data related to the risks of treatment are also lacking in the areas where we lack efficacy. This includes co-morbid insomnias, treatment with some of the most commonly administered insomnia agents, and longer-term treatment. With regard to the last, there has been one open-label study of year-long nightly dosing carried out in the elderly, demonstrating a favorable long-term safety profile with zaleplon 5–10mg [42].

Conclusions

Insomnia and its treatment with pharmacological therapy are very common in the elderly [1, 2, 3, 4]. However, at the same time, there are relatively few data on the risks and benefits of available therapies that are needed for making the types of empirically based decisions needed to optimize clinical practice. Areas where data are particularly lacking include:

1. whether treatment affects the insomnia-associated risks of falls/hip fractures, cognitive impairment, nursing home placement, and early mortality [5, 6, 7, 8, 9].
2. the effects of treatments on daytime functional impairments [17].
3. longer-term treatment data
4. data on insomnia occurring co-morbidly with medical and psychiatric conditions
5. data on more agents, particularly antidepressants, some of which appear to be used quite commonly in the elderly [28].

Owing to the relative lack of available data for many agents, dosages, and conditions, it is often necessary to turn to other sources of information when making treatment decisions in older adults. These include placebo-controlled studies carried out in younger adults, pharmacokinetic considerations, trials carried out with other agents of the same class, and trials carried out in other disorders. However, this should only be done with great caution due to the relatively greater risks of adverse effects in the elderly, which provide relatively little room for error when making such decisions. Owing to the greater likelihood of adverse effects in older adults, their slower medication elimination, and greater vulnerabilities, data from younger adults will be likely to underestimate the risks in the elderly. Simply prescribing a lower dosage than the dosage typically used in younger adults is also problematic because we lack the capacity to determine how much to lower the dosage, or even if there is a dosage that achieves efficacy and a reasonable safety profile in the elderly. This can only be determined on the basis of placebo-controlled trials.

Lacking clear guidance from data on whether treatment affects the risks of falls, nursing home placement, etc. [5, 6, 7, 8, 9], each clinician has to decide for themselves whether to take these risks into account. While there are few data on the effects of pharmacological treatment on daytime impairment in the elderly, those that exist suggest that treatment is likely to have an impact on daytime function. In terms of the absence of data in the elderly on co-morbid insomnia, clearly studies in this area are needed. Based on the available data from younger adults, it seems likely that the risk–benefit tradeoff observed in primary insomnia studies will be at least as favorable in co-morbid

insomnias [21, 22, 23, 24, 25, 26, 27]. However, this should not be assumed where other or more severe co-morbid conditions are concerned than those studied in younger adults or with medications other than those previously studied in the condition of interest (major depression, generalized anxiety disorder, post-alcohol discontinuation, rheumatoid arthritis, and chronic obstructive pulmonary disease).

Given the absence of data on the efficacy and safety of long-term pharmacotherapy with available agents in the elderly and lacking any means to determine how long to optimally treat any individual, it is necessary to take a practical approach [10]. One reasonable strategy is to make an agreement to carry out periodic trials of medication discontinuation (following a dosage taper if indicated) prior to initiating treatment with a medication for insomnia. Once a patient has been medication-free for several weeks a judgment can be made as to whether the treatment-associated benefits outweigh the side effects of treatment. In instances where the risk–benefit ratio is favorable, it is reasonable to continue the medication, whereas if the adverse effects outweigh the benefits, the treatment should be discontinued and alternative treatments should be considered.

Unfortunately, such strategies are a poor substitute for having the types of data needed to make optimal clinical decisions in older insomnia patients. Hopefully, such studies will be carried out in the near future and will provide an increasingly effective empirical basis for clinical risk–benefit assessments that will lead to improved treatment of insomnia in the elderly.

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Part 4
Chapter
32

Treatment of sleep disorders in the elderly

Epidemiology of sleep medication use in the elderly

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Introduction

History of sleep medication

Medication to help people sleep has been around for a long time. In the 1500s Paracelsus developed laudanum from opium [1]. Unfortunately, he was not aware of its addictive properties and, consequently, numerous people became addicted when in the eighteenth and nineteenth centuries laudanum use became widespread throughout Europe and the USA. Later, bromide compounds, e.g. potassium bromide, became popular as sedatives [2]. Subsequently, many other sedating medications of varying effectiveness, cost, and side effects emerged. Among these were the barbiturates, which although safer than the drugs used earlier, are still very addictive and dangerous in overdose and withdrawal. In the 1960s benzodiazepines (BZD) were hailed as a vast improvement, but even they were not immune to controversy, e.g. triazolam in the early 1990s [3]. Benzodiazepines are still the major hypnotics and sedatives on the market today but newer classes of medications are making inroads, such as the non-benzodiazepine benzodiazepine receptor agonists, including zolpidem, zaleplon, and zopiclone/eszopiclone [4]. These are often called z-hypnotics and the one most commonly used in Canada is zopiclone. Z-hypnotics are supposed to cause less disruption of normal sleep architecture, less psychomotor and memory problems, and less rebound insomnia [5]. Among other options for prescription sleep medications are sedating antidepressants, such as trazodone and amitriptyline.

There are also commonly used over-the-counter (OTC) sleep medications. Shelf space at drugs stores are filled with sleeping aids with suitable names such as Nytol, Sleep-eze, and Sominex. These contain mostly antihistamines with sedative effects, such as diphenhydramine and doxylamine. Another category of sleeping aids with increasing market shares are t he herbal products and other so-called natural products, including valerian, chamomile, kava kava, and homeopathic remedies, Most of which are also OTC. An exception is melatonin, which is a naturally occurring hormone produced during the sleep period for which a prescription is needed in some countries. Rozerem (ramelteon), which mimics melatonin, is a prescription insomnia medication approved by the FDA in 2005 and marketed to consumers in 2006. It has not been confirmed to what extent these actually improve sleep [6]. Safety and effectiveness have not been documented to any extent and these herbal products need to be evaluated further [5]. Another type of non-prescription substance traditionally used as a sedative is alcohol, especially by males [7, 8]. Alcohol has short-term sedative effects but is also a stimulant [9].

Objectives

In general, more information is needed about who takes what medication to help them sleep. A Canadian study called the Canadian Community Health Survey (CCHS) will be used to help address this issue in this chapter. Our objectives here will be formulated with the following epidemiological research questions guiding the discussion

WHO? Who are the people most likely to use medication to enhance sleep? What lifestyle factors, e.g. smoking, alcohol use, BMI, stress, and physical activity, are associated with sleep medication use?

WHERE? Does it make a difference where people live in terms of urban/rural or region of the country?

WHY? What reasons do people have to use medication to help them sleep? What proportion of people have characteristics, e.g. co-morbidity, that point to a reason for having difficulty sleeping?

WHAT type of sleep medication are they using? What are the differences between people taking a prescription and those taking over-the-counter medication?

Study population

Data from the CCHS cycle 1.2 will be used to provide the framework for discussing the epidemiology

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of sleep medication use. These data collected in 2002–2003 were based on a random sample of the Canadian population, and a source population of 9393 respondents over the age of 60 years was obtained. The interview included questions regarding the use of medication to help sleep and whether the medication used was OTC or prescribed. Sleep medication use was requested by the question: "In the past 12 months, that is from the date one year ago to yesterday did you use any medication to help you sleep, such as Imovane, Nytol, or Starnoc?" Sleep medication in terms of this particular question will be denoted as SM but a more general discussion of sleep medication will use the full term. The respondents were also asked whether the medication used was prescribed by a physician: "Did you take medication to help you sleep under the supervision of a health professional?" Further questions on type of health professional made it possible to limit the answer to physicians and specialists, such as psychiatrists. More precise drug use data but without reason for use was obtained by the question: "What medications did you take over the last two days?" Here respondents were asked to read the name of the drug from the label of its container. The drugs were coded with the Anatomic Chemical Therapeutic (ATC) classification originally developed by WHO [10] and adapted in Canada [11, 12]. Since zopiclone has a similar action to BZD and may be substituted for them, zopiclone was included with the BZD. The combination of these will be called BZD&Z. Other z-hypnotics were not available in Canada at this time.

Information on sleep medication

Thus, two different types of information were available to inform us on the use of sleeping pills in this population: one question asked about medication intended to help with sleep while the other asked about the use of medication which is known to be often used to help with sleep, e.g. BZD. The latter concept gives the researcher a sense of having more precise data and is, in fact, the information usually used in published studies. The former concept provides information about people who intend to take medications to help them sleep. While this is not a precise question about use of specific drug products, it is a more reliable question about motivation as to why the person used the drug. Respondents may or may not know what is in the medication they are taking, but they do know why they take the medication. This has several advantages. If one only has information on exact drug products without the motivation/indication, it is not always easy to tell why the product is used. For example, benzodiazepines are often used to help people sleep but are also used for anxiety, depression, restless legs syndrome, as muscle relaxants, for treatment of epilepsy, and for treatment of withdrawal symptoms. This is even more true for the OTC sleep products, which tend to be antihistamines used largely for other purposes such as allergic reactions.

Since we are able to present data for BZD&Z use alongside that for SM use, we will be able to compare the use of medications that people knowingly use with the intention to help them sleep with the specific medications that are known to be prescribed for helping with sleeping. Thus we will be able to compare the results of the present study with that of other studies, which usually rely on data on BZD use. Another advantage of this data was that the SM question also included OTC sleep medications and a further question allowed a distinction between the prescription and OTC medications. It is difficult to obtain data on OTC medications for large populations, and few studies include data on both prescription and OTC medications.

Issues with information on sleep medication

In spite of the considerable advantages of our data source already mentioned, there are also some limitations we need to take into consideration. For example, there may be some concerns about the differences in time frames covered by the two types of questions. The time frame for BZD&Z use in this study was the last 2 days before the interview while the time frame for the SM was any time in the last 12 months. This presents some difficulties in comparing the two types of questions; however, similar differences in time frame also occur in comparison with other studies and among other studies. While the different time frames would affect the absolute proportions of people taking these medications, these differences are not likely to be proportionally as large as the differences between the time frames themselves. For example, the proportion of people taking BZD&Z over the last 30 days would be nowhere near 15 times that of people taking BZD&Z over the last 2 days. It is known that a large proportion of sleep medication users have been taking them for years [13, 14]. These long-term BZD&Z/SM

users would be counted only once whether over the past 12 months or over the last 2 days. Consequently, the data is more comparable than might originally have been thought.

Another issue is that the question about prescribed SM does not take into consideration the possibility that people have taken both prescription and OTC medications over the past year. People who had used both prescription and OTC would have to say yes to the question: "Was it prescribed by a physician?" In this case the proportion of people using OTC medication may well be underestimated. However, other studies found that most people stayed with the same sleep medication in the long term and very few took both prescription and OTC sleep medication [14].

Sleep medication use

In our study of 9393 people over 60 years old, 17% reported taking SM over the last 12 months and 9% took BZD&Z within the last 2 days (Table 32.1). Furthermore, it was found that BZD users comprised 40% of all SM users and 45% of the prescription SM users. This latter proportion is about the same magnitude as the proportion of long-term users among BZD&Z users [13]. Of interest is that only 74% of people using BZD in the last 2 days had taken SM in the last year. If all BZD users used BZD to help them sleep, the answer should have been yes for 100%. Even allowing for some forgetfulness there is still a large proportion of people who took BZD&Z for some reason other than to help them sleep. This is not that surprising since there are many other indications for BZD&Z use. Thus, there should be concern about equating BZD use with sleep medication use. For this reason and because of comparability with other published studies, data is provided on both SM use and BZD&Z use to see what, if any, are the differences in attributes of their use.

Table 32.1. Sleep medication and BZD&Z use by seniors

Age	No. in population	No. of sleep medication (SM) or BZD&Z takers (%)
SM users among the source population		
Male	3764	487 (12.9)
Female	5629	1119 (20.2)
All	9393	1606 (17.1)
BZD&Z users among the source population		
Male	3764	252 (6.7)
Female	5629	610 (10.8)
All	9393	862 (9.2)
BZD&Z users among the subpopulation taking SM (Rx and OTC)		
Male	487	187 (38.4)
Female	1119	448 (40.0)
All	1606	635 (39.5)
BZD&Z among the subpopulation taking Rx sleep medication		
Male	412	181 (43.9)
Female	972	441 (45.4)
All	1384	622 (44.9)
SM users among the subpopulation taking BZD&Z		
Male	252	187 (74.2)
Female	610	448 (73.4)
All	862	635 (73.7)

The who, where, why, and what of sleep medication/BZD&Z use

WHO are the people most likely to use SM and/or BZD&Z?

To describe the "who" of sleep medication use, demographic characteristics and lifestyle factors were evaluated. According to Table 32.1, more women than men take SM (20% and 13%, respectively). This is also true for BZD&Z, which are taken by 7% of men and 11% of women. This agrees with other studies, regardless of how the use of sleep medication was measured [13, 15, 16, 17, 18]. No particular reason can be confidently given for this greater use of sleep medication by women, except that it is in line with the greater medication and healthcare use by women in general [13, 19]. Since depressive disorders occur more frequently in women, and since sleep disturbance is a common occurrence in depression, depressive disorders may provide a partial explanation.

Even within this population over the age of 60, sleep medication use increases with age (Table 32.2). Thus, seniors aged 80 and over are 2.6 times as likely to take BZD&Z compared to seniors aged 60–69 and 1.6 times as likely to take SM. In fact, one in five people over 80 took SM. Other studies have also found an increase of BZD use with age although most studies compare elderly people, e.g. over 65, with younger age groups rather than different age levels of the over 60s as in this study [13, 15]. The older seniors were also more likely to receive a prescription from their doctor to help them sleep rather than use OTC SM. This may well relate to the increasing chronic disease and other discomforts associated with age and the increasing likelihood of sleep issues with age even within the senior age groups [20].

This study found that people who were single, widowed, or separated i.e. without a partner, were 1.5 times as likely to take BZD&Z. Other studies reported that living without a partner also increased BZD&Z use in a younger population [15]. However, not having a partner does not appear to affect the use of SM in this age group, nor was the use of prescription SM compared to OTC any different from the average. One wonders if that means that people without a partner were taking BZD&Z for other reasons than sleep enhancement. For example, depressive and anxiety disorders, which may have a higher prevalence in those without a partner, could be treated with BZD.

Socioeconomic (SE) class is often defined by income level or education. This study found that neither income nor education levels in this elderly population seem to make much difference to SM use once adjusted for age. However, BZD&Z use in the lowest income quartile was almost double that of the highest quartile. Similarly for education, completion of high school did not affect SM use but did affect BZD&Z use, which was 40% higher for people who did not complete high school. Some other studies also found a greater frequency of BZD&Z use for those with lower levels of education [21] but others found the opposite to be true [13]. The difference between BZD&Z and SM use may imply that the increased BZD&Z use for lower SE class is not necessarily related to sleep but to other reasons for use of BZD&Z, such as depression or anxiety. Having insurance for medication costs did not seem to increase either BZD&Z or SM use in this study. In Canada, all residents over 65 have insurance for selected medications, which would include most commonly used prescription drugs but not OTC medication. Extra insurance cover would be useful in the 60–65 age group as well as for medication not covered by the provincial formularies in older age groups. People with lower income were more likely to take prescription SM than those in the higher income quartiles. An obvious reason may be the greater anxiety in coping on a low income, but another reason may be that for many people prescription medication is covered by their insurance while OTC medication is not.

Lifestyle factors potentially relevant to the use of these medications include stress, physical activity, smoking, and alcohol use. Suffering from stress was associated with both SM and BZD&Z use showing a 2.5- and 2.9-fold elevation, respectively, for those reporting and not reporting stress. Clearly stress is a considerable factor in sleep medication use. Here, one might have expected a bigger difference between BZD&Z and SM use since BZD&Z is also used for anxiety related to stress. Stressed people were more likely to take prescription SM than others. People who led a very sedentary lifestyle were more likely to use SM and BZD&Z, which may be related to an increased likelihood of having activity-limiting conditions. Thus, people with chronic disease may be more likely to have a sedentary lifestyle and may also be more likely to use BZD&Z and SM. BMI made little difference to BZD&Z or SM use although people of normal weight seem to have a somewhat higher use of SM.

Table 32.2. BZD&Z and sleep medication (SM) use in seniors: weighted for the Canadian population (2002)

Variables		Population[1]	BZD&Z use among the population[2]		Sleep medication (SM) use				
					Among the population[3]		Among those taking medication for sleeping[4]		
		%	%	OR	%	OR	Rx	OTC	Rx/OTC OR
All (N = 9393)		17.0	7.9		15.9		85.6	14.4	
Who									
Sex	Male	46.2	6.5	1.0	12.8	1.0	83.7	16.3	1.0
	Female	53.8	9.1	1.4*	18.6	1.5*	86.7	13.2	1.2
Age	60–69	49.8	5.7	1.0	13.2	1.0	80.8	19.2	1.0
	70–79	35.2	9.0	1.6*	17.9	1.4*	87.4	12.6	1.6*
	80+	15.1	12.4	2.6*	20.1	1.6*	92.2	7.6	2.9*
Partner	No	64.6	11.0	1.5*	14.8	0.9	88.2	11.8	1.0
Socioeconomic class									
Income quartiles	1st (low)	12.6	13.1	1.9*	18.8	1.2	92.7	7.3	3.0*
	2nd	29.8	8.7	1.3*	17.1	1.1	87.8	12.3	1.8*
	3rd	31.2	6.6	1.1	14.8	1.0	85.6	14.5	1.6*
	4th (high)	15.4	4.2	1.0	15.2	1.0	73.3	26.7	1.0
Insurance for Rx	Yes	75.9	8.1	1.1	16.2	1.1	85.6	14.4	1.0
Finish high school	Yes	46.6	8.1	1.0	15.0	1.0	81.2	18.8	1.6*
	No	53.5	9.3	1.4*	16.8	1.1	88.8	11.2	1.0
Lifestyle									
Stressed	Yes	12.2	16.5	2.9*	28.5	2.5*	87.7	12.3	1.4*
Smoking	Yes	17.8	9.8	1.5*	17.6	1.3*	84.8	15.2	1.2
Activity level	Inactive	51.4	10.3	1.8*	18.5	1.4*	88.1	12.0	1.5*
BMI	<25	44.5	8.2	1.0	15.0	1.0	88.6	11.4	1.3
	25–30	38.5	8.3	1.1	17.3	1.3*	83.3	16.7	0.9
	30+	17.1	6.2	0.8	15.1	1.1	84.0	16.0	1.0
Alcohol	9+drinks/wk	42.1	9.7	1.4*	17.4	1.2	88.5	11.5	1.5*
Where									
Rural/urban	Rural	19.3	7.8	1.0	14.7	0.9	82.8	17.2	1.2
Regions	Atlantic	8.0	9.5	2.3*	16.0	1.1	86.0	14.0	1.9*
	Quebec	25.6	10.7	2.8*	16.7	1.2	94.5	5.6	5.0*
	Ontario	38.5	7.0	1.7*	15.8	1.1	81.9	18.1	1.3*
	Prairies	14.6	7.8	1.8*	16.2	1.2	85.3	14.7	1.7*
	BC	13.4	4.5	1.0	14.4	1.0	78.2	21.8	1.0
Health-related									
Health status	Worse	56.3	11.4	3.5*	20.6	2.3*	90.2	9.8	3.4*
Depression	Yes	2.1	28.9	4.9*	44.9	5.9*	86.9	13.1	1.4
Allergies	Yes	27.6	10.0	1.4*	20.1	1.4*	85.1	14.9	1.1

Table 32.2. (*cont.*)

Variables		Population[1]	BZD&Z use among the population[2]		Sleep medication (SM) use				
					Among the population[3]		Among those taking medication for sleeping[4]		
		%	%	OR	%	OR	Rx	OTC	Rx/OTC OR
Arthritis	Yes	43.0	10.8	1.8*	20.1	1.6*	89.0	11.0	1.6*
Asthma	Yes	7.6	13.6	1.9*	21.5	1.4*	92.4	7.6	2.0*
Back problems	Yes	25.4	11.6	1.8*	24.0	2.1*	86.1	13.8	1.1
Cancer	Yes	5.7	10.4	1.4*	20.2	1.4*	94.9	5.1	3.1*
CVD	Yes	20.0	13.0	1.9*	23.1	1.8*	92.6	7.4	2.4*
Diabetes	Yes	12.6	8.1	1.1	17.6	1.2	90.8	9.2	1.7*
COPD	Yes	7.8	15.7	2.3*	23.4	1.6*	92.9	7.1	1.7*
Fibromyalgia	Yes	1.7	19.7	3.1*	39.4	3.5*	85.0	15.0	1.1
GI problems	Yes	5.3	13.9	2.0*	26.7	2.1*	89.8	10.2	1.7*
Painful conditions	Yes	54.0	10.2	1.9*	20.3	2.0*	88.1	11.9	1.8*
Any chronic condition	Yes	86.9	8.8	4.8*	17.5	3.2*	96.9	3.1	4.7*
	No	13.1	1.7	1.0	5.6	1.0	86.5	13.5	1.0
Concomitant medication									
Antidepressants	Yes	5.2	31.2	6.6*	57.0	8.5*	97.8	2.2	10.8*
CVD meds	Yes	10.3	39.6	13.7*	73.2	25.6*	91.5	8.5	2.2*
Herbal sleep products	Yes	1.1	2.1	0.2*	28.5	2.0*	64.8	35.2	0.3*

*Odds ratio (OR) is statistically significant at $p < 0.05$.

Note: Odds ratios (OR) (generated by logistic regression) adjusted for age and sex, will express the ratio of SM or BZD&Z use for a subgroup compared to the corresponding reference group. For example, for the age group 80+, an OR of 2.6 indicates that persons over age 80 are 2.6 times as likely to use BZD&Z as persons aged 60–69. Similarly, the over 80-year-olds are 2.9 times as likely to use SM as the youngest age group.

[1]Population %: percentage of people with that variable in the source population, e.g. 49.8% of source population weighted for the Canadian population is aged 60–69.

[2]Proportion of people in the category taking BZD&Z, e.g. 5.7% of people aged 60–69 take BZD&Z.

[3]Proportion of people in that category taking sleep medication, e.g. 13.2% of people aged 60–69 take sleep medication.

[4]Proportion of people taking Rx or OTC sleep medication, e.g. of people aged 60–69 80.8% are taking Rx SM and 19.2% are taking OTC medication.

Smokers and people who had more than nine alcoholic drinks per week were somewhat more likely to use BZD&Z and SM. Other studies have also found somewhat higher BZD&Z use in smokers [13]. Increased alcohol use with BZD&Z use may relate to the fact that alcohol has both stimulant and sedative effects. While one may fall asleep quicker, there is also the increased likelihood that one may wake up again within a few hours. Alcohol users were more likely to use prescription SM, which is consistent with Roehrs *et al.*'s finding that sleep loss associated with alcohol use was stronger than the sedative effect [9]. In spite of this, some studies indicate that a number of people use alcohol as a sleeping aid [22].

Where do people live?

An interesting question is the extent to which location of residence affects the use of SM/BZD&Z. According to the data in this study, urban or rural locations make little difference to either SM or BZD&Z use. On the other hand, regions of residence in Canada show great variation of BZD&Z use. The westernmost province,

British Columbia (BC), had by far the lowest BZD&Z use while the province of Quebec and the Atlantic Provinces had the highest BZD&Z use at more than double that of BC. Ohayon compared psychotropic drug use for sleep disorders in France with that in the province of Quebec and found that it was considerably higher in France than in Quebec [23]. Total SM use in this study was similar for all provinces but a huge variation was seen in the proportion of prescription SM with Quebec showing as much as five times the prescription use compared to BC while Atlantic provinces and the prairies were less than double the amount. Thus, although total SM use was comparable, the choice of OTC or prescription products varied greatly. It is hard to know how to explain this difference, but it seems to reflect a different pattern of prescribing by Quebec physicians.

Why do people use sleep medication?

The most obvious and most direct reasons for taking sleep medication would be because people have difficulty sleeping. The CCHS provided a number of questions about quality of sleep. One question asked whether respondents had trouble sleeping. More than one third of people having trouble sleeping reported taking SM, and of these, a somewhat higher proportion than expected was taking prescription SM (Table 32.3). Among those having trouble sleeping, four times as many reported taking BZD&Z as those not reporting trouble sleeping. Benca found that 24% of people with sleep difficulty used OTC sleep medicine [24], which is higher than the proportions in this study. Another puzzle is why 19% of people who rarely have difficulty sleeping are taking BZD&Z and 12% are taking SM (Table 32.3). One wonders why they take BZD&Z and/or SM if they have no difficulty sleeping. One can suppose that the BZD&Z is taken for other reasons. For SM users with a long time frame, it is possible that they had difficulty sleeping months ago but it is no longer a problem for them. It is also possible that the medication was effective in correcting sleep troubles they previously had.

Another question pertains to whether people find sleep refreshing. About one quarter of people reported that they rarely find sleep refreshing and an excess number of this group was found to be taking BZD&Z/SM. One may wonder whether the problem with refreshment from sleep occurs before or after taking the SM/BZD&Z: if before, then this is likely part of the reason why they are taking the sleep medication; if after, then these symptoms may represent an adverse effect of the medication. In the latter circumstance, respondents should probably explore other ways of dealing with their sleep problems. However, these clinical issues cannot be definitively clarified using epidemiological data. Only a small proportion of people have difficulty staying awake during times that they would like to be awake. This is somewhat higher for people who take either SM or BZD&Z but possibly not as much as one might expect. Again, daytime somnolence may be one of the reasons for taking one of these medications. There might also be an adverse side effect with some of these medications, particularly the long-acting ones.

The survey also asks about the number of hours people normally sleep each night. As one would expect, people sleeping less than 6 hours per night are the most likely to take SM/BZD&Z or SM. This group is also more likely to take prescription rather than OTC SM. More surprisingly, people sleeping more than 9 hours per night are also more likely to take BZD&Z/SM and are more likely to take prescription SM rather than OTC medication. One wonders whether this is a group of people who want to sleep for a large number of hours, perhaps motivated by chronic discomfort of some kind. Since the pattern is similar for both SM and BZD&Z one cannot attribute it to BZD&Z use for other reasons.

A more indirect reason for taking BZD&Z/SM would be chronic illness. Ancoli-Israel states difficulty falling asleep or staying asleep are among the most common complaints of elderly people [25, 26], but she does not think such complaints need to be inevitably associated with aging. She suggests that the complaints may be secondary to medical and psychiatric illnesses, their treatments, or other sleep disorders. This agrees with the results of this study (Table 32.2). People who feel that they are in poor health were found to be 3.5 times as likely to take BZD&Z and 2.5 times as likely to take SM with an increased proportion of them taking prescription SM. People with chronic conditions were also much more likely to be taking BZD&Z or SM. Patterns for BZD and SM consumption are fairly similar. The chronic condition with the largest proportion of SM and BZD&Z takers, other than depression, is fibromyalgia, being about three times higher than in non-takers. Fibromyalgia is a chronic condition that is notably associated with sleep disturbance. However, a two-fold increase in SM and BZD&Z use was also seen in those suffering from arthritis, back

Table 32.3. BZD&Z and sleep medication (SM) use by quality of sleep for seniors: weighted for the Canadian population (2002)

Variables		Population[1]	BZD&Z use[2]		Sleep medication (SM) use[3]				
		%	%	OR	%	OR	Rx %	OTC %	Rx/OTC OR
All			7.9		15.9		85.6	14.4	
How long do you usually spend sleeping each night?	<6 hrs	16.6	11.9	1.9	26.8	2.5*	89.9	10.1	2.0
	6–7 hrs	20.8	7.4	0.9	15.6	1.3*	81.0	19.0	1.0
	7–8 hrs	29.9	5.9	1.0	12.1	1.0	81.9	18.1	1.1
	8–9 hrs	24.7	6.6	1.4	13.3	1.1	86.6	13.4	1.5
	9+ hrs	7.9	12.2	1.8	15.9	1.3*	90.5	9.5	1.9
How often do you have trouble going to sleep or staying asleep?	Rarely	83.4	5.8	1.0	11.5	1.0	83.4	16.6	1.0
	Often	16.6	18.5	3.6*	38.1	4.6*	89.1	10.9	1.6
How often do you find your sleep refreshing?	Often	74.1	6.0	1.0	11.4	1.0	85.5	14.3	1.0
	Rarely	25.9	13.3	2.3	28.9	3.1*	85.8	14.2	0.9
How often do you find it difficult to stay awake when you want to?	Rarely	94.3	7.7	1.0	15.4	1.0	85.7	14.4	1.0
	Often	5.7	11.5	1.5	24.7	1.8	85.2	14.8	1.1

* Odds ratios (OR) are statistically significant at $p < 0.05$ and were generated by logistic regression, adjusted for age and sex.

[1]Population %: percentage of people with that variable in the source population, e.g. 16.6% of weighted source population for the Canadian population sleeps <6 hours per night.

[2]%: proportion of people taking BZD&Z, e.g. 11.9% of people sleeping <6 hours/night take BZD; OR: 1.9 times as many people who sleep <6 hours/night take BZD&Z than people who sleep 7–8 hours/night when adjusted for age and sex and weighted for the Canadian population.

[3]%: proportion of people taking SM divided into Rx or OTC sleep medication; OR: e.g. of people sleeping <6 hours/night and taking SM, twice as many take Rx sleep medication than take OTC sleep medication, weighted for the Canadian population.

problems, GI problems, cardiovascular disease (CVD), chronic obstructive pulmonary disease (COPD), and other painful conditions such as migraine headaches. The association with pain is not surprising [27]. People with any one of the chronic conditions listed above had a very high OR; however, this high OR is not so much because of the consumption of BZD&Z and SM by those with one or more chronic diseases but because of the low consumption by those without a chronic condition.

People with depression, which in this study means people who experienced a major depressive episode (according to the short-form version of the Composite International Diagnostic Interview) in the past year, were five times more likely to use BZD&Z and SM. Tu *et al*. found a decreasing use of BZD&Z in the 1990s by the elderly in Ontario, which was offset by an increase in use of antidepressants [28]. In our study we found a large proportion of BZD&Z and SM users (31% and 57%, respectively) were also taking antidepressants. This is not surprising since one of the more common symptoms of depression is difficulty sleeping; another one is anxiety. These results may indicate inadequate control of depressive symptoms as part of poor clinical outcomes from major depression treatment. Alternatively, antidepressant-induced sleep disturbances could play a role. It is possible that symptoms of depression in this age group are frequently mistaken for sleep disturbance, so that people with depressive disorders may receive symptomatic treatment for their sleep symptoms rather than more definitive treatment for the underlying depressive disorders.

Long-term use

The present study is largely based on cross-sectional data, which does not provide information on length of use. However, other studies have found that a large proportion of people taking SM/BZD take them over the long term [14, 17, 29]. A study on the epidemiology of long-term BZD&Z found that even though recommendations for BZD&Z use suggest durations of less than a few weeks, almost half of the population taking BZD&Z had been taking them for years [13]. Long-term users compared to all BZD&Z users were more likely to be female and elderly. It was found that by far the greatest predictor of future use was past use. The present study has some indication of similar proportions of long-term use, in that among people taking prescription SM at any time in the preceding 12 months, 45% were still taking BZD&Z in the past 2 days. Bartlett *et al*., after following a cohort of new users, found that 17% filled one or further prescriptions over a 5-year period and some showed long periods of use [29]. They also found that while the starting dose was often fairly low, it tended to increase with age. Over the time these BZD users were followed, 28.8% switched at least once and as many as 8.2% had more than one prescription at a time. Neutel found that while most long-term users stayed with the same BZD over a 2-year period, about a third changed to another BZD [13].

What types of SM are used: BZD versus SM, prescription versus OTC?

In spite of differences in time frame and type of question, the patterns of use of BZD&Z/SM and prescription or OTC SM, on the whole, tended to be consistent. The similarity was particularly evident in increased use for women with age, stress, smoking, physical activity, many chronic diseases, and depression. Where there were differences they could generally be explained; for example, the increase in BZD but not for SM use for lower income groups can be explained by the higher proportion of prescription use among lower income groups. Thus, although the total SM use is the same, the products are more likely to be on prescription. Similarly, the total SM use is comparable across different regions in Canada, but what varies greatly is the extent to which people use prescription medication to help them to sleep rather than OTC; the province of Quebec is an example of where there is excessive prescription SM use. Another group with a different pattern are those taking herbal products who have very low BZD use and a low prescription SM use. This makes sense since these people are using herbal products to help them sleep that are largely OTC. In addition, the qualities of sleep measures are answered similarly for BZD&Z use and SM even to the U-shaped patterns in the hours of sleep.

Implications

Appropriateness

From data such as those presented in this study it is difficult to draw conclusions about appropriateness of medication use. In this study 9% of the population over 60 took BZD&Z in the last 2 days before the interview, while 17% of the population took SM at sometime in the last 12 months. Another study showed that more than 20% of people over 65 in Ontario, Canada were dispensed BZD during a 12-month period [30]. This is a considerable use of this medication and it is not surprising that BZD are best sellers. The question then becomes: is this appropriate use? Determining appropriateness of BZD&Z use in a large population is much more difficult than just measuring use. Obviously, recommendations for duration of BZD use in drug monographs are exceeded when half of BZD users also reported use 2 years earlier [13]. It cannot be assumed that each and every one of these is inappropriate use, since BZD is an important tool in managing certain long-term illnesses. However, it stands to reason that there are many long-term users who would be better off not taking them, especially in the light of concerns about dependence and other adverse effects.

Dependence, addiction, and abuse

The terms dependence, addiction, and abuse are not always used consistently, nor with reference to formal diagnostic criteria such as those of the Diagnostic and Statistical Manual of Mental Disorders (DSM). Sometimes the terms are used synonymously with any long-term use, possibly because length of use is easier to measure in data from large populations than other definitions of dependence. More informatively, these terms have different meanings, e.g. abuse as "addictive non-medical use" [31], or dependence and addiction as referring to either or both of psychological/behavioral and physical dependence [32]. Withdrawal

effects and rebound effects, as have been commonly reported, would make quitting more difficult. Such withdrawal effects tend to be worse for shorter half-life BZD and for higher doses, but symptoms are expected to disappear in about 4 weeks [33, 34]. In a randomized controlled trial (RCT) of short-term BZD versus placebo use, Hajak *et al*. defined the rebound effect as a deterioration below pre-treatment values in some aspects of sleep quality or daytime well-being [32, 35]. The experience of a rebound effect may make patients feel that the drug is still effective even when it no longer is effective. Zopiclone is sometimes seen to have advantages over the BZD in terms of dependence and abuse potential [31]. Hajak indicated that although z-hypnotics are relatively safe, people with a potential for dependence could still have trouble with them. A study on long-term BZD use showed that in terms of long-term use zopiclone has a pattern similar to BZD [13].

An important question about long-term use is that of continued benefit. Many agree that there is a fair amount of tolerance developing after a time [36, 37, 38]. If SM remained effective, one might expect continued use to relate to reasonable indications for BZD use, a chronic condition where anxiety control or help with sleeping is needed on a longer-term basis, such as in depression or arthritis. The present study, as well as a previous study on long-term BZD use [13], indicated that overall BZD use correlates highly with many conditions that would seem to be plausible indications for BZD use. However, the study of long-term users showed that such indications become much less important with continued use [13]. The only variable that continues to show equal association over the years are migraine headaches. In studies where patients were asked why they wanted to continue taking SM, their answers still related to problems with sleeping rather than to specific conditions [38]. Sproule *et al*. found that patients felt that SM OTC continued to be effective even with long-term use [39]. Even so, the present study and others show that SM/BZD users still sleep less than non-users [38]. It is possible that the perception of benefit outweighs actual benefit. The beginning of withdrawal symptoms or rebound effect may give the appearance that there is still a benefit in spite of tolerance [35]. Mah and Upshur showed that there are differences in perception of long-term benefit in patients and their physicians in that patients are more likely to perceive benefit than their physicians think is likely [40].

Altering the use of sleep medicine

There have been numerous attempts at modifying long-term sleep medicine use, particularly BZD use for which most data is available. Voluntary programs to promote decreased use of BZD have not been very effective. When investigators tried to encourage a 3-week drug holiday, it was found that two-thirds of long-term low-dose patients rejected this idea [41]. Thus, patients already oppose discontinuation long before any withdrawal symptoms begin to show. Another study noted that 58% of BZD users had tried to stop but were unable to do so and that 50% of patients said they would like to quit but find it difficult [38]. Winkelman indicated that patients had a fear of the withdrawal effect [42], while Jefferson *et al*. found that most insomniacs practice poor sleep hygiene [43]. Health professionals may be influential, e.g. one study found that physicians tend to think of aging as a negative experience and considered long-term BZD use justified by the distress of their patients [44]. A study of physician education with the aim of reducing BZD use by elderly patients was not found to be effective [45]. Benca concluded that behavioral therapies are at least as effective in improving sleep and have longer-lasting effects than medication [24].

One way of modifying BZD usage is by means of regulation. In most countries prescriptions are needed for BZD&Z, however, requiring a prescription obviously does not prevent long-term use. Attempts at stricter regulation, such as triplicate prescribing, were tried in a number of places. One reason for triplicate prescribing has been the prevention of drug diversions and other illegal activities and has been found to be effective for that purpose [46]. Triplicate prescribing has also been found to be effective in reducing BZD use [46, 47, 48], but sometimes at the cost of increased use of other psychotropic products, such as barbiturates, meprobamate, and chloral hydrate [46, 47], which have even more undesirable qualities than BZD. Any attempt at stricter regulation needs to be done only after a consideration of what drugs might be substituted.

Conclusions

This article provides new information on the epidemiology of sleep medication use. One new development in this chapter is the comparison of sleep medicine taken for the express reason of helping with sleep with medication which often has the indication

of enhancing sleep while it is not known why it was actually taken. Another new development is the comparison of the use of OTC sleep medication with prescription sleep medication. Both of these new developments add to the available knowledge on the subject. While BZD is an important tool in treating many conditions and some long-term use is justifiable, everything possible should be done to prevent patients embarking on a path that they or their doctors may later wish they had not followed. Many previous articles on BZD use have called for the use of other, non-pharmacological ways of dealing with insomnia [49]. Winkelman stressed that there is a burden of treatment for insomnia and he reviewed a series of obstacles to adequate treatments such as outdated management guidelines [42]. More needs to be known about treating insomnia and Holbrook's call for research is worth repeating: "Given the importance of sleep for health and normal functioning, the diagnosis, prognosis and treatment of insomnia should be a research priority" [50].

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Part 4
Chapter
33

Treatment of sleep disorders in the elderly

Management of insomnia in the elderly: the efficacy and safety of non-benzodiazepine hypnotics

Jaime M. Monti and Daniel Monti

Introduction

Several facts have been established concerning sleep related to gender and age. The young adult spends 20–28% of a night's sleep (7–8 hours) in rapid eye movement (REM) sleep, 4–5% in stage 1, 46–50% in stage 2, 6–8% in stage 3, and 10–16% in stage 4 non-rapid eye movement (NREM) sleep [1]. Sleep stage amounts for males and females within the same age range are not significantly different. Total sleep time is longest in neonates and infants. In addition, the fastest decrease in sleep length is also observed during this period (from a mean of 16.6 hours in the newborn to 13.6 hours in the 6.5-month-old infant) and is apparently related to a sharp diminution of REM sleep. Marked declines in sleep duration are also observed from childhood to early adolescence (9.9 hours and 7.9 hours for mean ages 2.1 and 13.8 years, respectively). During maturity and old age a much slower but steady decline of sleep occurs [1].

Two other variables, stage 4 sleep and REM sleep, undergo profound changes with development. REM sleep (expressed in minutes) decreases sharply during early childhood. The decline tends to ease during late childhood, and then, after a plateau during adolescence and young adult years, REM sleep continues to diminish through maturity and old age. Stage 4 sleep amounts to 17.3% of total sleep time at age 2.6 years. This sleep stage decreases continuously throughout the lifespan, amounting to 4.5% of total sleep time at a mean age of 80 [1].

Prevalence of insomnia in the adult population

Insomnia is defined as the inability to get the amount or quality of sleep necessary for optimal functioning and well-being.

The 1991 National Survey of Sleep Complaints in the USA by the National Sleep Foundation in conjunction with the Gallup Organization, in which 1000 individuals were interviewed, showed that sleep-related complaints are common in the general population [2, 3]. Thirty-six percent of the subjects reported occurrences of insomnia during the course of the year. One in four of those experiencing insomnia stated that the complaint was chronic. The incidence of chronic insomnia was higher in older adults, who indicated that family-related stress and health-associated problems first precipitated their sleeping problem. Occasional insomniacs amounted to 27% of the sample, and they considered that work-related stress was the most frequent cause of their insomnia. More than half of the chronic insomniacs reported non-restorative sleep, fatigue, and impaired functioning during the daytime. Less frequently, the patients complained of frequent awakenings and difficulty falling asleep. In addition, 40% of the insomniacs reported snoring, which in some instances was related to obstructive sleep apnea. In order to improve their sleep chronic insomniacs relied on physical exercise, relaxation techniques, over-the-counter (OTC) medication, or alcohol.

In the study by Hohagen *et al*. [4], in which insomnia was assessed in 2512 patients by means of operationalized diagnostic criteria (DSM-III-R) [5], 18.7% had severe, 12.2% had moderate, and 15% had mild insomnia. Increased prevalence of insomnia with advanced age was the most pronounced in the group of patients with severe insomnia, and in this group, women prevailed significantly.

In the Upper Bavarian Field Study a total of 1536 subjects were interviewed to determine the prevalence of insomnia [6]. Twenty-eight percent of the sample suffered from insomnia during the week prior to the interview (mild 15%, moderate/severe 13.5%). Prevalence rates were significantly higher among women and the older age groups. In addition, moderate/severe insomnia was strongly related to psychiatric and medical health problems and the use of psychiatric in- and outpatient services and general hospitals. Moreover,

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48.5% of the subjects suffering from moderate/severe insomnia used hypnotic and/or other psychotropic drugs during the week preceding the interview.

In the 1990 Cross National Medication Survey, conducted in the United States and eight Western European countries, adult respondents were interviewed using a standard questionnaire and the Hopkins Symptom Checklist. Prevalence rates of mild insomnia varied by country from 23% to 51%. The prevalence of severe insomnia in the same populations varied from 10% to 28%. Serious problems with insomnia appeared in individuals of all ages, were more frequent in women than in men (58 versus 42%), and became more pronounced with age [7].

Lugaresi *et al.* [8] conducted a study that included 5713 inhabitants of the Republic of San Marino. The study authors found that 13.4% of the sample were poor sleepers and that 19.1% of the population suffered from insomnia. Reasons given for difficulty sleeping included worries, aches, and trouble with breathing. Complaints of depression, anxiety, gastrointestinal disturbances, and headaches were reported more often by insomniacs than by good sleepers. Among insomniacs, 11.4% made use of sleeping pills habitually and 21.7% only occasionally.

Thus, most studies performed in the United States and Europe have reported similar percentages of insomnia.

Insomnia in elderly subjects

Foley *et al.* [9] made use of the baseline and 3-year follow-up data from the EPESE studies conducted by the National Institute of Aging [10] to assess the frequency of sleep complaints in over 9000 subjects aged 65 years and older. Between 23% and 34% of the participants experienced symptoms of insomnia. Seven and 15% of these patients rarely or never, respectively, had restorative sleep. Insomnia was associated with an increased number of physical disabilities, respiratory symptoms (chronic coughing, wheezing, or phlegm), OTC medication use, depressive symptoms, and poorer self-perceived health. Interestingly, advanced age generally was not associated with more frequent sleep complaints after adjusting for health status. In other words, sleep disturbances in the elderly were likely caused by chronic disease rather than the aging process per se.

More recently, Foley *et al.* [11] performed an epidemiological study of 6800 elderly adults over 3 years to determine incidence and remission rates of insomnia. At the first interview 4956 subjects did not complain of insomnia. On the other hand, nearly 15% of the sample reported symptoms of insomnia that were associated with heart disease, stroke, hip-fracture, diabetes, depressive mood, or respiratory symptoms. In addition, most of these patients made chronic use of hypnotic medication. Among the survivors with sleep difficulties during the first interview, 932 no longer complained of insomnia 3 years later, and this was related to the successful treatment of their somatic or psychiatric diseases. The study authors concluded that age was not a factor in the remission of insomnia, and that a sleep disorder may not always be a chronic state in the elderly.

Disorders associated with chronic insomnia

Primary insomnia

Primary insomnia is a complaint of difficulty initiating and maintaining sleep or of non-restorative sleep that lasts for at least 1 month and causes clinically significant distress or impairment in social, occupational, or other important areas of functioning [12]. If the insomnia is precipitated or aggravated by another sleep disorder or mental disorder, or is due to the direct physiological effects of a substance or a general medical condition, then the other disorder is termed primary and the insomnia secondary, or co-morbid [12, 13].

Primary insomnia includes a number of insomnia diagnoses in the International Classification of Sleep Disorders (ICSD) [14], among them, psychophysiological insomnia, sleep state misperception, idiopathic insomnia, and some cases of inadequate sleep hygiene. Psychophysiological insomnia most closely resembles primary insomnia. Patients with a diagnosis of psychophysiological insomnia react to an emotional trigger or precipitating event that may be stressful with somatized tension and agitation. The further development of sleep-preventing associations precludes patients from falling asleep when desired. Individuals with idiopathic or childhood-onset insomnia show a lifelong inability to obtain adequate sleep; there is no evidence of medical or psychiatric disorders that could account for the sleep disturbance. In both psychophysiological and idiopathic insomnia, polysomnography demonstrates that stage 2 sleep latency and the number of nocturnal arousals are increased, whereas total sleep time is reduced. The main difference between idiopathic and psychophysiological

insomnia is the age of onset: childhood for the former and young adulthood for the latter. Bonnet and Arand [15] contend that patients with psychophysiological or idiopathic insomnia suffer from a disorder of hyperarousal and that the elevated arousal is responsible for the disrupted sleep.

Sleep state misperception is a condition characterized by complaints of insomnia with a marked discrepancy between subjective and objective estimates of sleep. Chronic insomnia related to inadequate sleep hygiene refers to insomnia resulting from: scheduling exercise too close to bedtime, performing activities demanding high levels of concentration shortly before going to bed, taking excessive daytime naps, or keeping irregular sleep hours. Increases in waking and decreases in total sleep time during nocturnal sleep are frequent findings.

In sleep disorder centers about 15% of all insomniacs are diagnosed with psychophysiological insomnia. The prevalence of idiopathic insomnia in its pure form is not known, whereas the incidence of sleep state misperception would be less than 5% of all patients with a complaint of insomnia.

Secondary, or co-morbid, insomnia

As stressed by McCrae and Lichstein [16] co-morbid insomnia is the most frequent form of insomnia. According to the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV) [12] co-morbid insomnia is that related to another mental disorder, another sleep disorder, a general medical condition, or the effects of a drug of abuse or a medication. The International Classification of Sleep Disorders (ICSD) [14] distinguishes 19 medical and psychiatric disorders that may lead to co-morbid insomnia. They include, among others, the psychoses, mood disorders, anxiety disorders, alcoholism, dementia, parkinsonism, fatal familial insomnia, sleep-related epilepsy, sleep-related headaches, nocturnal cardiac ischemia, chronic obstructive pulmonary disease, sleep-related asthma, sleep-related gastrointestinal reflux, peptic ulcer, and fibromyalgia. It should be pointed out that several well-known diseases and medications responsible for the occurrence of co-morbid insomnia have been omitted in the ICSD (see Table 33.1).

Lichstein [13] recognizes three varieties of secondary insomnia: (1) absolute secondary insomnia, when the onset and the course of the insomnia coincide with that of the other disorder; (2) partial secondary insomnia, in which either the onset or the course of the insomnia mimics that of the mental disorder, the medical condition, or the symptoms induced by a drug of abuse, a medication, or a toxin; and (3) specious secondary insomnia, in which the sleep disorder and the primary condition are simply co-morbid.

In a patient with excessive anxiety and worry related to generalized anxiety disorder, absolute secondary insomnia is diagnosed if the insomnia appears shortly after the beginning of the underlying mental disorder and improves or worsens in parallel with its course. Partial secondary insomnia is diagnosed when the insomnia appears in individuals who subsequently develop anxiety and follows the course of the underlying disorder.

Profiles of therapeutic hypnotic agents: benzodiazepines, zopiclone, eszopiclone, zolpidem, and zaleplon

Insomnia is a multidimensional disorder, and any approach to its management should combine non-pharmacological measures, sleep hygiene education, and pharmacotherapy. In practice, pharmacological treatment of chronic primary insomnia predominates over psychotherapy and other treatment methods. In patients with chronic insomnia and a co-existing psychiatric, neurological, or medical condition, the underlying disorder needs to be treated appropriately.

Several classes of medications have been prescribed as hypnotics over the years. The benzodiazepines (BZDs) were introduced in the 1970s and rapidly increased in popularity because of their efficacy and relative safety compared with the barbiturates, carbamates, chloral derivatives, and methaqualone [17]. However, the risk of dependence, the occurrence of rebound insomnia following the withdrawal of short- and intermediate-acting derivatives, and the loss of efficacy after a few weeks of treatment led to a decrease in their use in recent years. The reduction in BZD hypnotic use has coincided with the introduction of a structurally dissimilar group of non-benzodiazepine (non-BZD) derivatives, such as the cyclopyrrolone agents zopiclone and eszopiclone, the imidazopyridine derivative zolpidem, and the pyrazolopyrimidine compound zaleplon [18].

Site and mechanism of action

The $GABA_A$ receptor is the site of action for compounds such as BZD and the non-BZD hypnotics zopiclone, eszopiclone, zolpidem, and zaleplon. These

Table 33.1. Disorders associated with chronic insomnia in elderly patients

Primary insomnia
Secondary or co-morbid insomnia
Determinants of secondary insomnia:
1. Mental disorders
1.1 Anxiety disorders
1.2 Depressive disorders
1.3 Schizophrenia and other psychoses
2. Neurological disorders
2.1 Alzheimer's disease
2.2 Parkinson's disease
2.3 Sleep-related epilepsy
2.4 Stroke
2.5 Sleep-related headache
3. Medical conditions
3.1 Cardiovascular diseases
3.1.1 Angina pectoris
3.1.2 Myocardial infarction
3.1.3 Congestive heart failure
3.1.4 Arterial hypertension
3.2 Respiratory disorders
3.2.1 Chronic obstructive pulmonary disease
3.2.2 Sleep-related asthma
3.2.3 Interstitial lung disease
3.3 Gastrointestinal diseases
3.3.1 Gastroesophageal reflux
3.3.2 Peptic ulcer disease
3.4 Endocrine diseases
3.4.1 Hypothyroidism
3.4.2 Hyperthyroidism
3.4.3 Diabetes mellitus
3.5 Neoplastic diseases
3.6 HIV infection
3.7 Rheumatic diseases
3.7.1 Rheumatic arthritis
3.7.2 Fibromyalgia
3.8 Menopause
4. Substance-induced sleep disorders
4.1 Methylxantines
4.2 Nicotine
4.3 Antidepressants
4.4 Antiepileptic drugs
4.5 Antihypertensive agents
4.6 Corticosteroids
4.7 Cocaine
4.8 Amphetamines

different classes of hypnotic drugs modulate GABAergic function through different $GABA_A$ receptor subtypes, defined by the subunits that participate in the receptor assembly. The majority of $GABA_A$ receptors consist of α, β, and γ subunits, which contain multiple isoforms or variants: α_1–α_6, β_1–β_3, and γ_1–γ_3. Zolpidem and zaleplon preferentially bind α_1-containing subtypes [19]. On the other hand, BZDs, zopiclone, and eszopiclone bind to all $GABA_A$ subtypes. Notwithstanding the above, the mechanism of action of the cyclopyrrolone derivatives may not be identical to that of the BZD hypnotics. In this respect it has been proposed that the cyclopyrrolones might have more selectivity for certain subunits of the $GABA_A$ receptor [20].

Pharmacokinetic aspects

The hypnotic drugs currently available for the treatment of chronic primary insomnia differ significantly in their pharmacokinetic properties, including elimination half-life ($t_{½}$) and presence of active metabolites. On the other hand, they share short absorption and distribution times. As a result, in most circumstances they induce sleep rapidly. According to their $t_{½}$, hypnotics can be divided into short-, intermediate-, or long-acting derivatives. Zopiclone, eszopiclone, zolpidem, and zaleplon are short-acting derivatives (Table 33.2).

Zopiclone 7.5 mg administered by oral route at night-time is rapidly absorbed. Peak plasma concentrations (T_{max}) are achieved in 0.5 to 1.5 hours. The compound undergoes oxidation to the *N*-oxide metabolite, which is pharmacologically active, and demethylation to the inactive *N*-desmethyl-zopiclone. The $t_{½}$ values of zopiclone and of its active metabolite are 3.5 to 6.0 hours [21]. Eszopiclone, the dextrorotatory enantiomer of racemic zopiclone, has a single chiral center with an S(+)-configuration [22]. Eszopiclone is rapidly absorbed and extensively distributed in body

Table 33.2. Elimination half-life, time to onset, and active metabolites for cyclopyrrolone, imidazopyridine, and pyrazolopyrimidine hypnotics

Drug	Elimination half-life (hours)	Time to onset (minutes)	Active metabolite
Zopiclone	3.5–6.0	15–30	*N*-oxide derivative
Eszopiclone	6.0	15–30	(*S*)-zopiclone-*N*-oxide
Zolpidem	2.0–2.5	30	No
Zaleplon	1.0	15–30	No

tissues, *including* the brain. T_{max} is attained in 1.0–1.6 hours after a single therapeutic dose of 3 mg, and $t_{½}$ amounts to approximately 6.0 hours. Eszopiclone is metabolized in the liver to form (*S*)-*N*-desmethylzopiclone and (*S*)-zopiclone-*N*-oxide. The metabolic clearance of zopiclone and eszopiclone is reduced in elderly subjects, aged 65 years and older, which results in increases in maximum plasma concentration (C_{max}) and $t_{½}$, the latter amounting to approximately 9.0 hours [20]. Thus, a dose adjustment is required in elderly patients.

Zolpidem is rapidly absorbed after oral administration, and t_{max} is attained 30–60 minutes after a single therapeutic dose of 10 mg. The major metabolic routes in humans include oxidation and hydroxylation, and none of the metabolites are pharmacologically active. The $t_{½}$ of zolpidem in healthy volunteers is 2.0 to 2.5 hours [23]. The metabolic clearance of zolpidem is reduced in elderly patients, aged 65 years and older, resulting in increases in C_{max}, the area under the concentration curve (AUC), and $t_{½}$, the latter amounting to approximately 2.9 hours [24]. Thus, a reduction of the initial dose from 10 to 5 mg in the elderly is indicated.

Zaleplon is rapidly and almost completely absorbed following oral administration of a 10 mg dose. T_{max} is approximately 1 hour and $t_{½}$ is 1 hour. Zaleplon is primarily metabolized by aldehyde oxidase, and all of its metabolites are pharmacologically inactive [25, 26]. The pharmacokinetics of zaleplon in elderly subjects does not appear to be significantly different from that in young healthy adults; however, this conclusion is only tentative because of the absence of adequate studies in this area [27]. Thus, a dose of 5 mg is recommended for elderly patients to decrease the risk of side effects.

Treatment efficacy

Overview of the effects of non-BZD hypnotics on sleep in non-elderly patients

The evaluation of the effect of hypnotic drugs on sleep induction and maintenance in non-elderly patients with chronic insomnia has been based on sleep laboratory studies and subjective data from clinical trials. When considering the results of clinical trials that made use of the clinical approach, it should be taken into consideration that patients with insomnia tend to overestimate the degree of their sleep difficulty. In addition, the reliability and the interpretation of results can be affected by patients' estimates of hypnotic drug effects, which are quite variable because of the influence of recent, as well as past, experiences with other sleep medications.

Zopiclone 7.5 mg per night is effective in inducing and maintaining sleep in patients with chronic primary insomnia. The increase in total sleep time is related to larger amounts of NREM sleep. No significant changes have been observed in REM sleep duration or as a percentage of total sleep time, although REM latency may be delayed [28, 29, 30]. In healthy young subjects, zopiclone decreases stage 1 sleep and increases stages 2 and 3 sleep or stages 3 and 4 combined [31, 32]. However, in adults with insomnia, zopiclone increases, decreases, or has no effect on stage 3 and/or stage 4 sleep as a percentage of total sleep time [21, 33]. No development of tolerance was observed in studies of zopiclone that lasted up to 4 weeks [34] (Tables 33.3 and 33.4).

The subjective perception of improved sleep following eszopiclone 2 or 3 mg treatment has been demonstrated in randomized, double-blind, placebo-controlled studies of up to 6 months' duration that included non-elderly patients. In these studies the drug significantly reduced sleep onset latency, the number of awakenings, and wake time after sleep onset, whereas total sleep time and quality of sleep were increased [35, 36]. Sleep laboratory studies of the effects of eszopiclone have confirmed the drug's clinical efficacy in subjects with chronic primary insomnia. Eszopiclone, unlike BZD hypnotics, did not significantly alter values of slow wave sleep (SWS) or REM sleep (Tables 33.3 and 33.4).

Polysomnographic studies in poor sleepers and non-elderly patients with chronic primary insomnia

Table 33.3. Effects of cyclopyrrolone, imidazopyridine, and pyrazolopyrimidine hypnotics on sleep parameters in patients with chronic primary insomnia

Variable	Zopiclone	Eszopiclone	Zolpidem	Zaleplon
Sleep induction:				
Stage 2 NREM sleep latency	Decrease	Decrease	Decrease	Decrease
Sleep maintenance:				
Number of awakenings	Decrease	Decrease	Decrease	or decrease
Wake time after sleep onset	Decrease	Decrease	Decrease	No change
Total sleep time	Increase	Increase	Increase	No change
Sleep quality	Improvement	Improvement	Improvement	No change
Sleep architecture:				
Stage 2 sleep	Increase	Increase	Increase	No change
Slow wave sleep (stages 3 and 4)	Decrease	No change	No change	No change
REM sleep	No change or decrease	No change	No change	No change
Long-term administration:				
Tolerance	Absent[1]	Absent	Absent	Present[2]
Discontinuation syndrome:				
Rebound insomnia	Present	Absent	Absent	Absent

[1]The potential for tolerance during long-term treatment remains unclear.

[2]In the study by Elie *et al*. [47], the effect of zaleplon 5 mg on sleep latency was lost by week 4.

have shown that zolpidem administered at a dosage of 10 mg at night for 4 weeks significantly increased sleep duration and diminished time awake after the onset of sleep. Stage 2 sleep latency was also reduced. Zolpidem markedly increased the duration of stage 2 sleep without significantly affecting or increasing SWS [37, 38, 39, 40]. The duration and the latency of REM sleep occurrence were not significantly modified after zolpidem (10 mg) administration [38, 39]. No evidence of tolerance was observed in long-term (3–13 months) studies [41, 42]. In addition, the potential for the development of tolerance with zolpidem 10 mg/day used "as needed" is very low [43] (Tables 33.3 and 33.4).

Table 33.4. Dosages of hypnotics used in the treatment of chronic primary insomnia

	Dosage (mg/night)	
Drug	Adult	Elderly
Zopiclone	7.5	3.75
Eszopiclone	2–3	1–2
Zolpidem – immediate release	10	5
Zolpidem – extended release	12.5	6.25
Zaleplon	10	5

A number of studies have shown that immediate-release zolpidem increases sleep duration only during the first half of the night. The drug effectively improves difficulty initiating sleep, whereas its sleep-maintaining effect is observed only during the first 4 hours after administration. This has led to the development of an extended-release formulation of zolpidem, which consists of a coated two-layer tablet: one layer that releases its drug content immediately and another layer that allows a slower release of the compound. The $t_{½}$ of immediate-release zolpidem is similar to that obtained with extended-release zolpidem. However, the latter provides an efficacious plasma drug concentration that lasts longer than 4 hours after administration. The clinical efficacy of extended-release zolpidem has been compared with placebo in adults with chronic primary insomnia [44]. During the 3 weeks of nightly treatment, extended-release zolpidem improved sleep maintenance over the first 6 hours of sleep; in addition the latency to persistent sleep was decreased. Rebound insomnia was noted during the first night following withdrawal of the active medication.

Adult outpatients with chronic primary insomnia have been evaluated in studies that compared the effects of zaleplon at doses of 5 or 10 mg with placebo on sleep variables. Polysomnographic and subjective assessments have indicated that zaleplon significantly reduces the time needed to fall asleep. Estimates of total sleep time and number of awakenings did not differ significantly between placebo and zaleplon. Zaleplon did not affect NREM sleep stages or REM sleep [25, 45, 46]. Tolerance to the sleep-inducing effect of zaleplon did not occur in the polysomnographic study by Walsh *et al.* [46], in which zaleplon 10 mg was given during 35 nights. However, tolerance developed to the reduction of sleep latency after the repeated administration of a 5-mg dose of zaleplon [47] (Tables 33.3 and 33.4).

Effects of non-BZD hypnotics on sleep of elderly patients

Two principal techniques have also been employed to evaluate the effects of zopiclone, eszopiclone, zolpidem, and zaleplon on sleep in elderly patients with chronic insomnia. One of the techniques made use of questionnaires (clinical approach) whereas the other involved utilization of a sleep laboratory. Two patient populations were included in the studies detailed in Tables 33.5, 33.6, 33.7, 33.8, 33.9, 33.10, 33.11 and 33.12 – outpatients with insomnia and hospitalized neuropsychiatric patients. The use of the latter is somewhat problematic. Insomnia in patients with neuropsychiatric disorders should, for the most part, be addressed by treatment of the underlying disease.

Although studies on the effect of non-BZD hypnotics on sleep in elderly insomniacs tended to generate consistent findings, methodological shortcomings limit the conclusions of some of them, namely, small number of subjects and such confounding variables as gender or phase of illness. In most clinical trials and sleep laboratory evaluations that involved elderly patients with insomnia, no use was made of an objective, systematic method of classifying their sleep disturbance. In other words, the nature of their sleep complaint was not well characterized. The effects of medication merit special concern. In this respect, some patients included in several studies were taking medications that could have modified the effect of the non-BZD hypnotics. In other studies an adequate washout period between drugs was lacking. Obstructive sleep apnea, periodic limb movement disorder, restless legs syndrome, and sleep disorders related to medical conditions, such as Parkinson's disease and Alzheimer's disease, are prevalent in older people. These aspects were not considered in some studies.

Zopiclone 5 or 7.5 mg given for periods ranging from 1 night to 5 weeks improved sleep in elderly insomniac patients, as judged by significant reductions in sleep latency and the number of nocturnal awakenings, and by the increase of sleep duration. Sleep quality and daytime alertness were also improved in most studies [48, 49, 50, 51]. Flurazepam 15 mg, triazolam 0.25 mg, nitrazepam 5 mg, or temazepam 15 mg tended to improve sleep in a fashion similar to that observed after zopiclone 7.5 mg [48, 49, 50, 51, 52]. Polysomnography performed during 1 night after 7.5 mg zopiclone showed an increase of stage 2 sleep and a reduction of wake time after sleep onset [52] (Tables 33.5 and 33.6).

Scharf *et al.* [53] and McCall *et al.* [54] assessed the effect of intermediate-term eszopiclone administration in elderly subjects with chronic primary insomnia. The study by Scharf *et al.* [53] was completed by 210 subjects who were given either placebo or eszopiclone 1 or 2 mg/night for 2 weeks. Eszopiclone 2 mg was effective in reducing sleep onset latency and wake time after sleep onset, whereas total sleep time was increased and sleep quality and depth, daytime alertness, and quality of life were improved compared with placebo. The efficacy of eszopiclone 1 mg was limited to a reduction of sleep onset latency (Table 33.7). The study by McCall *et al.* [54] was completed by 255 subjects who received either eszopiclone 2 mg or placebo for 2 weeks. The subjects spent nights 1, 2, 13, and 14 in the sleep laboratory and reported efficacy measures during nights 1 to 14. The effects of eszopiclone 2 mg on sleep induction and maintenance are summarized in Table 33.7. Eszopiclone administration significantly reduced the latency to persistent sleep and the wake time after sleep onset, whereas total sleep time and sleep efficiency showed significant increments. This hypnotic drug significantly increased stage 2 sleep, whereas stage 1, stages 3 and 4, and REM sleep were not significantly modified. Subjective evaluation was relatively well correlated with the sleep laboratory findings.

Zolpidem 5 or 10 mg given to elderly patients for periods ranging from 1 night to 6 months significantly reduced sleep onset latency and the number of nocturnal awakenings, and increased sleep duration. The quality of sleep and daytime alertness were also improved [55, 56, 57, 58, 59, 60, 61, 62, 63]. Similar effects were obtained in comparative studies in which triazolam 0.125 mg, temazepam 15 mg, or

Table 33.5. Effects of zopiclone on sleep of elderly patients with insomnia

Elie and Deschenes [48]	Venter *et al*. [49]	Klimm *et al*. [50]
Study design:		
Double-blind, cross-over	Double-blind, multicenter	Double-blind
Number of patients:		
30 outpatients (M = 8; F = 22)[1]	41 outpatients (M = 10; F = 31)	72 outpatients (M = 15; F = 57) (71 patients had concomitant medical conditions)
Mean age (years):		
75.0 ± 1.8 (range 60–93)	76.8 (range 60–96)	73.2 ± 1.5
Dosage (mg/night):		
Zopiclone 5, 7.5, or 10 mg or flurazepam 15 mg or placebo 4 nights per week for 5 weeks (when required chloral hydrate was given on weekends)	Zopiclone 7.5 mg or triazolam 0.25 mg for 10 nights preceded by placebo	Zopiclone 7.5 mg or nitrazepam 5 mg for 7 nights preceded and followed by placebo (concomitant treatments were administered to 71 patients)
Assessment of sleep:		
Questionnaire	Questionnaire	Spiegel Sleep Questionnaire; psychometric tests
Sleep latency:		
Decrease[2] (in the four groups; zopiclone 7.5 and 10 mg similar to flurazepam 15 mg)	Decrease[2] (with both treatments)	Decrease[2] (with both treatments)
Number of nocturnal awakenings:		
–	Decrease[2] (with both treatments)	–
Sleep duration:		
Increase[2] (in the four groups)	Increase[2] (in the two groups)	Increase[2] (in the two groups)
Sleep quality:		
Improved[2]	Improved[2] (with both treatments)	Improved[2] (with both treatments)
Daytime alertness:		
Not modified	Improved[2] (with both treatments)	–
Adverse events:		
The incidence was found to be similar for the five treatments	Reported by 20 patients receiving zopiclone and 8 patients receiving triazolam	Reported by 2 patients in each group; 1 patient on nitrazepam withdrew from the study
Rebound insomnia:		
–	–	–
Tolerance:		
–	–	–

[1]M = male; F = female.

[2]Significantly different from placebo.

flunitrazepam 1 mg were administered to insomniac patients [58, 59, 64]. In the studies in which 20 or 30 mg zolpidem was given to elderly insomniacs, adverse events were frequent and severe, and drop-outs were markedly increased [55, 59, 62, 65]. In the polysomnographic study by Kummer *et al.* [66] zolpidem 20 mg induced a reduction of stage 1 sleep, whereas stages 2 and 3 and REM sleep were significantly increased (Tables 33.8, 33.9, 33.10 and 33.11).

The limited amount of information pertaining to the effect of zaleplon on sleep in elderly insomniacs indicates that this hypnotic drug given at a dose of 5 or

Table 33.6. Effects of zopiclone on sleep of elderly patients with insomnia

Elie *et al.* [51]	Hemmeter *et al.* [52]
Study design:	
Double-blind, parallel group	Double-blind, cross-over
Number of patients:	
44 inpatients (M = 11; F = 33)[1]	12 outpatients (M = 6; F = 6)
Mean age (years):	
76 ± 1.3 (range 60–90)	65.9 ± 3.6 (range 60–70)
Dosage (mg):	
Zopiclone 5 mg or triazolam 0.125 mg or placebo during the first week; zopiclone 7.5 mg or triazolam 0.25 mg or placebo for the next 2 weeks; the double-blind phase was preceded and followed by placebo	Zopiclone 7.5 mg or temazepam 20 mg or placebo during 1 night each
Assessment of sleep:	
Questionnaire	Polysomnography (1 adaptation night and 3 study nights separated by 1 week each)
Sleep latency:	
Decrease[2] on week 2 after triazolam 0.25 mg	Decrease[2] after temazepam
Number of nocturnal awakenings:	
–	Decrease[2] (with both treatments)
Wake time after sleep onset:	
–	Decrease[2] (with both treatments)
Sleep duration:	
n.s.[3]	Increase[2] after temazepam
Sleep architecture:	
–	Increase of stage 2 sleep[2]
Quality of sleep:	
n.s.	Improvement after zopiclone[2]
Adverse events:	
Reported by 5 patients who received zopiclone and 1 patient who received placebo	Psychomotor and memory performance were not significantly altered after zopiclone or temazepam
Rebound insomnia:	
–	–
Tolerance:	
–	–

[1]M = male; F = female.

[2]Significantly different from placebo.

[3]n.s. = non-significant.

10 mg during 2 to 7 nights decreases sleep latency and the number of nocturnal awakenings. Ancoli-Israel *et al.* [67] reported in addition an increase of sleep duration. However, their finding could not be confirmed by Walsh *et al.* [46] (Table 33.12).

Adverse events in adult and elderly patients

Zopiclone (3.75–7.5 mg) and eszopiclone (1–3 mg) exhibit an adverse event profile that is somewhat similar

Table 33.7. Effects of eszopiclone on sleep of elderly patients with chronic primary insomnia

Scharf *et al*. [53]	**McCall *et al*. [54]**
Study design:	
Randomized, double-blind, placebo-controlled	Randomized, double-blind, placebo-controlled
Number of patients:	
231 (210 completed the study)	264 (255 completed the study)
Mean age (years):	
72.3 (range 64–85)	71.1
Diagnostic criteria:	
DSM-IV criteria for primary insomnia	DSM-IV criteria for primary insomnia
Dosage (mg/night):	
Placebo (N = 80); eszopiclone 1 mg (N = 72) or 2 mg (N = 79) for 2 weeks	Placebo (N = 128); eszopiclone 2 mg (N = 136) for 2 weeks
Assessment of sleep:	
Interactive voice response system	Polysomnography : nights 1, 2, 13, and 14; patient reports: nights 1 to 14
Objective sleep parameters	
Sleep induction	
NREM sleep latency:	
–	Decrease[1]
Sleep maintenance	
Number of awakenings:	
–	n.s.[2]
Wake time after sleep onset:	
–	Decrease[1]
Total sleep time:	
–	Increase[1]
Sleep efficiency:	
–	Increase[1]
Sleep architecture	
Stage 1 sleep:	
–	n.s.
Stage 2 sleep:	
–	Increase[1]
Slow wave sleep:	
–	n.s.
REM latency:	
–	–
REM sleep (min):	
–	n.s.
REM sleep (% of total sleep time):	
–	Increase[1]
Subjective sleep parameters	

Table 33.7. (*cont.*)

Scharf *et al*. [53]	**McCall *et al*. [54]**
Sleep latency:	
Decrease (1 and 2 mg)[1]	Decrease[1]
Number of awakenings:	
–	Decrease[1]
Wake time after sleep onset:	
Decrease (2 mg)[1]	Decrease[1]
Total sleep time:	
Increase (2 mg)[1]	Increase[1]
Quality of sleep:	
Increase (2 mg)[1]	Increase[1]
Rebound insomnia:	
–	–
Tolerance:	
–	–

[1]Significantly different from placebo ($p < 0.05$).

[2]n.s. = non-significant.

Table 33.8. Effects of zolpidem on sleep of elderly patients with chronic insomnia

De Domenico *et al*. [56]	**Schlich *et al*. [62]**	**Fairweather *et al*. [63]**
Study design:		
Single-blind, placebo-controlled	Single-blind, placebo-controlled	Double-blind, three-way, cross-over
Number of patients:		
39 outpatients (M = 26; F = 13)[1]	107 outpatients	24 outpatients
Mean age (years):		
65 (range 60–81)	63 (61% over 60 years of age)	>60
Dosage (mg):		
Zolpidem 10 mg during 3 weeks preceded and followed by placebo	Zolpidem (flexible dose 10–20 mg) during 6 months preceded and followed by placebo	Zolpidem 5 or 10 mg or placebo
Assessment of sleep:		
Questionnaire and sleep diary	Questionnaire	Leeds Sleep Evaluation Questionnaire
Sleep latency:		
Decrease[2]	Decrease (80% of patients)	Decrease
Sleep duration:		
Increase[2]	Increase (70% of patients)	Increase
Number of awakenings:		
Decrease[2]	Decrease (47% of patients)	–
Quality of sleep:		
Improved[2]	–	Improved

Table 33.8. (*cont.*)

De Domenico *et al.* [56]	Schlich *et al.* [62]	Fairweather *et al.* [63]
Daytime alertness:		
Improved[2]	–	Not impaired
Adverse events:		
Reported by 4 patients	Reported by 24 patients	Similar number of adverse events in the three groups
Rebound insomnia:		
Absent	Absent	–
Tolerance		
–	Not detected	Not detected

[1]M = male; F = female.

[2]Significantly different from placebo.

Table 33.9. Effects of zolpidem on sleep of elderly patients with chronic insomnia

Ochs *et al.* [64]	Dolenc *et al.* [57]	Leger *et al.* [60]
Study design:		
Double-blind, multicenter, placebo-controlled, parallel group	Double-blind, multicenter	Single-blind, multicenter
Number of patients:		
355 outpatients	50 outpatients with primary insomnia according to DSM-IV (M = 11; F = 39)[1]	769 outpatients (75% of patients also had a medical condition)
Mean age (years):		
range 59–85	74 ± 8	72.9 (range: 65–100)
Dosage (mg)		
Zolpidem 5 mg or temazepam 15 mg or triazolam 0.125 mg or placebo for 4 weeks preceded and followed by placebo	Zolpidem 5 mg or triazolam 0.125 mg during 2 weeks preceded and followed by placebo	Zolpidem (flexible dose 5–10 mg) during 27 nights (74% of the patients also took medication for their medical condition)
Assessment of sleep		
Questionnaire	St. Mary's Sleep Questionnaire, Stanford Sleepiness Scale, Visual Analog Scale for Sleep Quality	Questionnaire and sleep diary
Sleep latency:		
Decrease[2] (with zolpidem and temazepam)	Decrease[2] (both treatments)	Decrease[2]
Number of nocturnal awakenings:		
n.s.	Decrease[2] (only after zolpidem)	Decrease[2]
Sleep duration:		
n.s.[3] (except for temazepam during week 2)	Increase[2] (both treatments)	Increase[2]
Quality of sleep:		
n.s.	Improved[2] (both treatments)	Improved[2]

Table 33.9. (*cont.*)

Ochs *et al.* [64]	Dolenc *et al.* [57]	Leger *et al.* [60]
Daytime alertness:		
–	Improved[2] (only after zolpidem)	Improved[2]
Adverse events:		
The incidence was not different across treatment groups	–	64 patients reported adverse events
Rebound insomnia:		
–	–	–
Tolerance:		
Not detected	Not detected	–

[1]M = male; F = female.

[2]Significantly different from placebo.

[3]n.s. = non-significant.

Table 33.10. Effects of zolpidem on sleep of elderly patients with chronic insomni

Emeriau *et al.* [59]	Roger *et al.* [55]	Shaw *et al.* [65]
Study design:		
Double-blind, multicenter, parallel group	Double-blind, multicenter, parallel group	Double-blind, parallel group
Number of patients:		
84 inpatients (M = 15; F = 69)[1]; 78 patients had a diagnosis of primary insomnia	111 inpatients (M = 30; F = 81)	119 neuropsychiatric inpatients
Mean age (years)		
83.1 ± 1.3 (range 61–95)	78 (range 61–94)	74.5 (range 65–85)
Dosage (mg)		
Zolpidem 10 mg (N = 28) or 20 mg (N = 27) or flunitrazepam 1 mg (N = 29) during 4 weeks preceded and followed by placebo	Zolpidem 5, 10, 15, 20, or 30 mg or placebo during a single night	Zolpidem 10 or 20 mg or placebo during 3 weeks preceded and followed by placebo (the patients were allowed to continue the treatment for their neuropsychiatric condition)
Assessment of sleep:		
Questionnaire	Questionnaire	Questionnaire
Sleep latency:		
Decrease[2] (in all three groups)	Decrease[2] (after 10 mg and above)	n.s.[3,4]
Number of nocturnal awakenings:		
Decrease (in all three groups)	Decrease (after 10 mg and above)	n.s.[4]
Sleep duration:		
Increase[2] (in all three groups)	Increase[2] (after 10 mg and above)	Increase[2] (after 10 mg and above)
Sleep quality:		
Improved[2] (in all three groups)	n.s.	n.s.[4]
Daytime alertness:		
Improved (72% of patients on zolpidem 10 mg; 63.2% of patients on zolpidem 20 mg; 58% of patients on flunitrazepam 1 mg)	n.s.	Disrupted in several patients who were taking zolpidem 20 mg

Table 33.10. (*cont.*)

Emeriau *et al.* [59]	Roger *et al.* [55]	Shaw *et al.* [65]
Adverse events:		
Observed in 20 patients	Adverse events were frequent and severe in the zolpidem 30 mg group	3 patients on placebo, 4 patients on zolpidem 10 mg, and 7 patients on zolpidem 20 mg had adverse events
Rebound insomnia:		
Absent	Absent	Absent
Tolerance:		
–	Not detected	Not detected

[1]M = male; F = female.

[2]Significantly different from placebo.

[3]n.s. = non-significant.

[4]Marked placebo effect.

Table 33.11. Effects of zolpidem on sleep of elderly patients with chronic insomnia

Kummer *et al.* [66]	Roger *et al.* [58]	Biondi and Casadei [61]
Study design:		
Single-blind	Double-blind, multicenter	Double-blind, multicenter
Number of patients:		
14 psychiatric inpatients	221 inpatients	285 neuropsychiatric inpatients (M = 101; F = 184)
Mean age (years):		
67.8 ± 2.2 (range 59–85)	range: 58–98	72.5 ± 6.1
Dosage (mg):		
Zolpidem 20 mg during 179 nights preceded and followed by placebo (10 patients continued treatment for their psychiatric condition)	Zolpidem 5 or 10 mg or triazolam 0.25 mg during 3 weeks preceded and followed by placebo	Zolpidem 10 mg for at least 7 nights preceded and followed by placebo (treatment for the neuropsychiatric condition could be continued)
Assessment of sleep:		
Polysomnography on nights 37, 97, and 187, and 90 days after stopping therapy	Questionnaire, Visual Analog Scale; Clinician's Global Impression	Questionnaire, sleep diary, Visual Analog Scale
Sleep latency:		
n.s.[1]	Decrease[2]	Decrease[2]
Number of nocturnal awakenings:		
–	Decrease[2] (in all three groups)	Decrease[2]
Sleep duration:		
Increase[2]	Increase[2] (in all three groups)	Increase[2]
Sleep architecture:		
Stage 1		
Reduction[2]	–	–
Stage 2		
Increase[2]	–	–
Stage 3		
Increase[2]	–	–
REM sleep (min)		

Table 33.11. (*cont.*)

Kummer *et al.* [66]	Roger *et al.* [58]	Biondi and Casadei [61]
Increase[2]	–	–
Sleep quality:		
–	Improved[2] (in all three groups)	Improved[2]
Daytime alertness:		
–	–	Improved[2]
Adverse events:		
Mild adverse events	Reported by 16% of patients on zolpidem 5 mg; 11% on zolpidem 10 mg, and 21% on triazolam 0.25 mg	Reported by 37% of patients
Rebound insomnia:		
–	–	–
Tolerance:		
–	Not detected	–

[1]n.s. = non-significant.

[2]Significantly different from placebo.

Table 33.12. Effects of zaleplon on sleep of elderly patients with chronic insomnia

Ancoli-Israel *et al.* [67]	Walsh *et al.* [46]
Study design:	
Double-blind, multicenter	Double-blind, multicenter
Number of subjects:	
549 outpatients with a diagnosis of primary insomnia according to DSM-IV (M = 231; F = 318)[1]	48 outpatients
Dosage (mg):	
Zaleplon 5 or 10 mg or zolpidem 5 mg or placebo for 2 weeks preceded and followed by placebo	Zaleplon 2.5, 5, or 10 mg or placebo; each treatment was given for 2 consecutive nights with sequences separated by a washout period of 5 to 12 nights
Assessment of sleep:	
Questionnaire	Polysomnography and post-sleep questionnaire
Sleep latency:	
Decrease[2] after zaleplon 10 mg and zolpidem 5 mg during weeks 1 and 2, and after zaleplon 5 mg during week 2	Decrease[2] with all three zaleplon doses; subjective sleep latency was reduced significantly with zaleplon 5 or 10 mg
Number of nocturnal awakenings:	
Decrease[2] with zolpidem 5 mg during both weeks	n.s.[3]
Sleep duration:	
Increase[2] after zaleplon 10 mg during week 1, and after zolpidem 5 mg during both weeks	n.s.
Sleep architecture:	
–	No treatment-related differences in the amount of stage 1, stage 2, slow wave sleep, or REM sleep; REM latency showed a dose-dependent increase

Table 33.12. (*cont.*)

Ancoli-Israel *et al*. [67]	**Walsh *et al*. [46]**
Sleep quality:	
Improved[2] after zaleplon 10 mg during the first week, and after zolpidem 5 mg during both weeks	–
Adverse events:	
Greater frequency with zolpidem	Psychomotor tests conducted the morning after each polysomnography showed no deficits with zaleplon
Rebound insomnia:	
Present after zolpidem	–
Tolerance:	
Not detected	–

[1]M = male; F = female.

[2]Significantly different from placebo.

[3]n.s.=non-significant.

to that of the shorter-acting BZDs. The most commonly reported side effects are unpleasant or bitter taste, followed by headache, dyspepsia, pain, diarrhea, dry mouth, dizziness, tiredness, and accidental injury [68, 69]. Zopiclone and eszopiclone also impair memory within the first few hours after administration [70, 71].

The most commonly observed adverse events associated with the use of immediate-release zolpidem (5–10 mg) are headache, drowsiness, dizziness, nausea, diarrhea, and myalgia [72]. During treatment with extended-release zolpidem (at daily doses of 6.25–12.5 mg) the most commonly observed events were somnolence, headache, and dizziness.

Adverse events occurring among zaleplon (5–10 mg)-treated patients include abdominal pain, asthenia, headache, dyspepsia, nausea, dizziness, and somnolence [72].

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Part 4
Chapter
34

Treatment of sleep disorders in the elderly

Use of benzodiazepines in the aging population: do the benefits outweigh the risks?

Malcolm H. Lader

Introduction

The benzodiazepine anxiolytics were introduced from about 1960 onwards. They were followed by benzodiazepines marketed as agents for treating sleep difficulties. In the past 20 years, compounds have been developed and marketed as hypnotics that are not chemically benzodiazepines but are pharmacologically very similar to them. They comprise the so-called "z-drugs," zopiclone, zolpidem, and zaleplon. In this chapter, the benzodiazepines and the z-drugs under the pharmacological rubric of "benzodiazepine-receptor agonists" (BDZras) are reviewed.

The pharmacological treatment of insomnia in the elderly has been reviewed in the previous chapter. In this chapter the analysis will be confined to a single question that has been debated for many years: do the risks of the BDZras outweigh the benefits in the elderly? Secondary questions are how that relates to the severity of the disorder, namely primary insomnia, and are alternatives available and preferable? They become salient considerations if the risk–benefit ratio of the BDZras is judged to be negative in the elderly. If the ratio is clearly negative, then these drugs should not be used as drugs of first choice but relegated to stand-by status. If the risk/benefit is strongly adverse, they should not be used except under the most exceptional circumstances.

The definitive review and meta-analysis

Usoa Busto's group in Toronto published a coruscating, detailed, critical review of 24 studies dealing with short-term treatment with sedative hypnotics in older people with insomnia [1]. Reference should be made to that review for a quantitative analysis of the data. The authors caution that:

1. All the sedatives were grouped together for analysis, irrespective of differences in dosages or duration of action.
2. Various outcome measures were used, encompassing ordinal, visual analog, and combined scales.
3. Although objective (polysomnographic) measures are more precise and reliable, the meta-analysis concentrates on subjective outcome measures "because consumption of healthcare resources is driven by subjective report rather than objective measures of sleep."
4. The health status of the subjects varied from community-dwelling, ambulatory patients to inpatients on a geriatric ward. This might affect responses to subjective assessments.
5. The sedative effects might compromise blinding.
6. Long-term use with tolerance, habituation, and dependence potential were not addressed because of practical limitations.

This author regards the formal quantitation as exhaustively addressed in that publication. However, there are qualitative considerations that might temper the conclusions and this chapter will be used to address those.

Clinical issues

The phenomenology and epidemiology of sleep disorders in the elderly are discussed in numerous other chapters in this book. Insomnia, the indication for BZDra hypnotics, is the most common disorder of sleep. Chronic insomnia occurs in about 10% of the general population but the prevalence rises with age: about 20% of the over 65s complain of insomnia, most often difficulty in maintaining sleep [2, 3]. The disorder may be primary, in which no clear etiology is apparent, or secondary to other disorders such as pain and cough. The incidence of these disorders rises steeply in the elderly.

The importance of insomnia in the elderly has been stressed [4]. In line with an increased prevalence of insomnia, the use of hypnotic medication rises steeply. This age-related increase in sleep disturbance is more pronounced in men.

Principles and Practice of Geriatric Sleep Medicine. ed. S.R. Pandi-Perumal, J.M. Monti, and A.A. Monjan.
Published by Cambridge University Press.

Opinions differed as to whether enhanced sensitivity to drugs in the elderly reflects pharmacokinetic differences or hypersensitivity of tissues in the elderly. In one study [5], the effects of nitrazepam 10 mg were compared with those of placebo in the over 65s and the under 40s. Both groups slept better on the drug. The elderly, despite having similar plasma concentrations of nitrazepam and similar elimination half-lives, were more psychometrically impaired. This suggests enhanced brain sensitivity.

A review of various aspects of insomnia in the elderly includes a section on pharmacological treatments [6]. It draws attention to the fact that after being initially "very effective," benzodiazepines produce a rapid development of tolerance, and are associated with numerous adverse effects in the elderly. Such problems include rebound, addiction, daytime sedation, dizziness, falls, hip fractures, and traffic accidents. Long-acting drugs are best avoided.

Chronic insomnia

This has been a contentious issue for many years. BZDras (except for eszopiclone recently) are licensed for short-term use of usually not more than 2–4 weeks. The DSM-IV criteria for primary insomnia include duration of at least a month. Thus, unless the hypnotic is "curative", relapse is inevitable when it is withdrawn. This means that prescribers lapse into long-term "ex-label" prescribing, with the practical, ethical, and legal complications that that entails. In particular, the problems of withdrawal and dependence with the BZDras become insistent.

A change of attitude was seen in the National Institutes of Health State-of-the-Science Statement of August 18, 2005 [7]. A meeting of experts concluded that chronic insomnia is a major public health problem, but that little is known of its mechanisms, causes, clinical course, co-morbidities, and consequences. Both cognitive-behavioral therapy (CBT) and BZDras were deemed efficacious, at least in the short term. But few data have accrued from very long-term trials. It is recommended that long-term studies of both positive and adverse effects extend to the period after discontinuation of treatment. Measures of daytime function and quality of life should be included, as well as the traditional parameters such as sleep onset latency and total sleep time. This authoritative review devotes little space in general to insomnia in the elderly, but it notes that many studies have shown a greater prevalence of insomnia among older people. The section on treatments states that the adverse effects of benzodiazepine receptor agonists appear to be worse in the elderly. The consensus asserts that the frequency and severity of the adverse effects are much lower for the newer agonists, most likely because these agents have shorter half-lives.

Some individual studies

Short-acting BZD hypnotics

Midazolam is a very short-acting sedative benzodiazepine widely employed as an anesthetic induction agent [8]. A comparison of midazolam 15 mg with an antihistamine-barbiturate combination in 39 elderly insomniacs showed the two medications to be equivalent in efficacy. However, the polypharmacy preparation caused hangover and accumulation.

Medium-acting BZD hypnotics

Brotizolam is a popular benzodiazepine hypnotic in some countries. Thirty-six subjects with sleep problems aged 60–72 were assigned to receive brotizolam 0.25 mg, flurazepam 15 mg, or placebo during a 2-week period [9]. Sleep was assessed using a subjective scale, and a battery of psychomotor tests was applied the next morning. Sleep improved with all treatments and significant effects were found. Rebound insomnia was detected on brotizolam withdrawal, but less so after discontinuing flurazepam. Indeed, only the group given placebo were sleeping longer than at baseline. Morning-after improvements were detectable on the first day after administration but then waned. The investigators concluded that: "The results of this study affirm the increased sensitivity of elderly subjects to benzodiazepine hypnotics and their indication for acute or intermittent insomnia, rather than for the more chronic forms of this disorder."

Lormetazepam 0.5 mg and 1 mg were compared in 145 elderly insomniacs in a double-blind non-placebo controlled study [10]. Sleep diaries were used. Both groups improved significantly over baseline. The higher dose was associated with more improvement according to a physician's rating at the end of the 7-night treatment course. Only 6% of patients in each group reported adverse effects – mostly hangover sedation. It was concluded that the lower dose was adequate.

Hypnotic efficacy, tolerance, and psychomotor effects were assessed for 0.5 mg or 1 mg of loprazolam or placebo in 89 elderly inpatients [11]. The treatments

were given double-blind, using a parallel design, for 5 nights. Sleep improved in all groups, as assessed by self-rating scales. Loprazolam was superior to placebo with respect to measures of sleep latency, satisfaction with sleep, number of nocturnal awakenings, and feeling refreshed on waking. Both doses had equal effects. The incidence of unwanted effects was low. Hangover effects were sought using tests such as choice reaction time and critical flicker fusion but were not detected.

Long-acting BZD hypnotics

The long-acting hypnotic, quazepam was compared with placebo in 57 geriatric outpatients complaining of insomnia [12]. The design was double-blind with random 5-night allocation. Assessment was by means of post-sleep questionnaires. Quazepam was significantly better than placebo on a range of measures, both with respect to quantity and quality of sleep. Quazepam was no different from placebo in terms of morning hangover, nor did it cause ataxia. Efficacy was maintained over the 5 nights.

Roth and his colleagues [13] compared quazepam 7.5 mg and 15 mg with placebo in 30 insomniac patients over the age of 60. After 2 nights of placebo the drug was given double-blind for 7 nights, followed by 2 more nights of placebo. Both doses increased total sleep time on the PSG with minimal effect on sleep staging. Plasma concentration measures showed persistence of desalkylquazepam so some effects were carried over to the subsequent placebo nights. Adverse effects reported were minimal.

BZDras ("z-drugs")

Twenty-four healthy elderly (mean age 71) volunteers with a perceived sleep onset latency of at least 30 minutes were given zolpidem 5 mg, zolpidem 10 mg, or placebo for 7 days in a double-blind, three-way, cross-over study [14]. The following morning after nights 1 and 7 they were assessed using a comprehensive battery of psychomotor tests. These comprised choice reaction time, tracking, critical flicker fusion, memory, and hand recognition. Sleep was assessed subjectively using the Leeds Sleep Evaluation Questionnaire and Linear Analog Rating Scales. With respect to "getting to sleep," both doses of zolpidem produced a significant effect as compared to placebo, but no difference was detected between the two doses. Quality of sleep was also improved. These subjective effects did not wane over the 7 days of each dose of active treatment. None of the psychomotor tests showed any impairment with zolpidem. The totals of self-reports of unwanted effects were 38 for the placebo, 47 with 5 mg, and 57 with the 10 mg of zolpidem. Severity also increased, but these trends did not reach significance. The authors concluded that zolpidem improves onset and quality of sleep in elderly subjects, without a "morning-after" effect.

Eszopiclone, the active *S*-enantiomer of racemic zopiclone has been licensed in the USA. A comprehensive review [15] of the drug noted two trials in the elderly. Erman *et al.* [16] allocated 264 insomniacs aged 65–85 to treatment with eszopiclone 2 mg or placebo nightly for 2 weeks. Both PSG and interactive voice response system data were collected. Over the 2-week period, eszopiclone significantly decreased objective LPS and WASO (wake after sleep onset), compared with placebo; sleep efficiency was significantly increased. Subjectively reported sleep latency, WASO, and TST were also improved by the drug over placebo. No rebound effects were noted following discontinuation. The most commonly reported adverse effect was unpleasant taste, about 20% compared with 7% in placebo-treated patients.

A second study [17] used two doses of eszopiclone – 1 and 2 mg – as compared with placebo, over 2 weeks in 231 elderly insomniacs. An IVRS system was again used. The primary outcome variable was sleep latency: 2 mg eszopiclone improved this compared with placebo (36.2 vs. 50 minutes); WASO and quality and depth of sleep were also significantly better. Eszopiclone 1 mg was less consistently effective.

A total of 437 patients over the age of 65 with primary insomnia were allocated to 2 weeks treatment with zaleplon 5 mg, zaleplon 10 mg, or placebo in a multicenter, double-blind, randomized study [18]. Post-sleep questionnaires were used to record sleep latency, sleep duration, number of awakenings, and sleep quality. At both doses zaleplon reduced subjective sleep latency, whereas only the 10 mg dose significantly improved sleep quality in terms of number of responders. Some rebound was detected after discontinuing the 10 mg dose, but no differences in treatment-emergent adverse events were apparent. This study used a large number of patients and some efficacy was found at the 5 mg dose, but more consistently after 10 mg; by contrast adverse events were unaffected.

Clomethiazole

Clomethiazole has long had the reputation for being safe and effective in the elderly. It has an elimination half-life of about 4 hours. In one study, 62 elderly

inpatients with complaints of insomnia received clomethiazole 384 mg , lormetazepam 1 mg, or placebo for 7 nights in a double-blind, double-dummy, placebo-controlled trial [19]. Both drugs significantly reduced sleep latency, increased sleep duration, and improved quality of sleep and feelings on awakening. Reaction times were unimpaired the next morning, and there was no clinical evidence of accumulation over time.

Comparative studies

A very relevant risk–benefit ratio study was conducted by Cook and his colleagues [20]. The hypnotic and residual effects of nitrazepam 5 mg, temazepam 20 mg, and placebo were measured over 7 months in 58 elderly inpatients (but not primarily insomniac). Two-thirds of both drug groups reported sleeping well, as compared with the third given placebo. These effects had worn off by the seventh night. Reaction time was unaffected after the first dose but substantially impaired by the morning after the 7th dose, although the patients had largely recovered by the afternoon. A letter-cancellation test was impaired even after the first doses and markedly so after the seventh dose of nitrazepam. Patients with low IQs were apparently most affected.

Another study concentrated on the adverse effects of two hypnotics, nitrazepam 2.5 mg and triazolam 0.125 mg, in a group of 18 elderly hospitalized patients with symptoms of insomnia [21]. Both drugs were judged to be effective hypnotics. Patients reported difficulty waking even after the lower dose of nitrazepam; after 5 nights' usage, psychomotor impairment ensued. Triazolam was accompanied by no such effects. The authors conclude: "If a benzodiazepine hypnotic is used in the elderly, a drug with a short elimination half-life is an advantage."

A comparison of triazolam, flurazepam, and placebo was carried out in 41 geriatric outpatients suffering from insomnia [22]. The doses were 0.25 mg triazolam and 15 mg of flurazepam and each treatment was given using double-blind procedures over 28 nights. Triazolam improved sleep onset, quality, and duration of sleep, and feelings of restfulness the next day. Flurazepam was superior to placebo only with respect to onset and quality of sleep. No evidence of tolerance was detected.

The hypnotic efficacies of 1.0 mg loprazolam and 5.0 mg nitrazepam were compared in 40 elderly patients (over 65) [23]. A double-blind parallel-group randomized trial design was used, and the drugs were given for 7 nights. Both medications significantly improved sleep patterns as assessed by self-rating scales and night nurses' global assessments, in comparison with placebo baseline screen. Both getting to sleep and quality of sleep according to patients' rating were improved. Nurses' ratings were similar. Wakening the next morning was not impaired. Failure to show significant difference between the two drugs is acknowledged by the authors to be due to the: "relatively insensitive and highly subjective nature of the assessments."

In a double-blind, placebo-controlled crossover study, triazolam 0.25 mg was compared with nitrazepam. Each was given for 2 weeks to geriatric patients in four homes for the aged in Gothenburg and one ward of a geriatric hospital [24]. Sleep quantity and quality were recorded by a nurse interviewing each patient the next morning. Psychomotor performance was assessed using the letter–cancellation test and the digit symbol test. Hand muscle strength was also measured. Side effects were elicited using a standardized questionnaire with specific questions across a range of functions. Both sleep quantity and quality were similar in the two drug administrations. Around 80–90% of the patients found the hypnotics helpful. Performances in the psychomotor tests were similar, as were reports of side effects. The study is under-powered but the two benzodiazepines appeared to have similar effects, despite their different durations of action.

Ten aged insomniac patients received either triazolam 0.25 mg or zopiclone 7.5 mg over 15 nights [25]. PSG recordings showed an improvement in sleep patterns. Delta sleep was decreased by triazolam, but increased by zopiclone.

Zopiclone 5 mg was compared to flunitrazepam 1 mg in a multicenter, double-blind, randomized, parallel group study, performed in 107 physically ill insomniac patients in Sweden [26]. The patients noted their sleep patterns in a diary. No differences between the drugs were found, except that patients given flunitrazepam fell asleep more quickly.

In a double-blind study in 44 elderly insomniac patients living in residential homes, zopiclone 5 mg up to 7.5 mg was compared with triazolam 0.125 mg with flexible increase to 0.25 mg, and placebo [27]. At the end of 3 weeks of double-blind administration, a 4-day single-blind washout placebo phase to assess withdrawal effects was added. Each patient was interviewed daily by the same research nurse in order to fill out a post-sleep questionnaire. The main drug effects

during the 3 weeks of treatment were an improvement in sleep latency with both drugs as compared with placebo, and in sleep soundness for zopiclone as compared with placebo. Morning wake-up and hangover effects did not differ. Withdrawal of triazolam was accompanied by a significant increase in sleep latency, and decrease in sleep soundness. Zopiclone showed no significant effects.

Zolpidem has been formulated as a modified release preparation. A study in normal healthy elderly volunteers compared doses of 6.25 and 12.5 mg with 30 mg of flurazepam, and placebo [28]. Ease of falling asleep and sleep quality were significantly improved by both active agents. Psychometric performance the next day was significantly impaired by flurazepam but by neither dose of zolpidem-MR.

Two controlled trials evaluated clomethiazole in the elderly. In the first, 40 patients aged 65–90 with sleep problems were treated double-blind in a crossover design with clomethiazole 384 mg or temazepam 20 mg each for a week [29]. Nursing staff observed the effects after the night's sleep. Some psychomotor tests were applied the next morning. Both drugs reduced time to sleep onset. On stopping the medication, clomethiazole showed rebound effects, whereas some carry-over effects were seen after temazepam. Sleep duration showed similar effects. Temazepam produced more adverse effects than clomethiazole.

The same research team compared clomethiazole with triazolam in 53 residents of an old people's home [30]. All had complained of sleep disturbance. The design of the study was a double-blind, parallel group with randomized allocation to clomethiazole base, 384 mg, or triazolam, 0.125 mg, over 9 weeks. In short-term use both drugs were effective. At endpoint at 9 weeks, only clomethiazole retained its earlier effectiveness at 6 weeks according to the nurses' assessment. Neither critical flicker fusion nor choice reaction time showed any consistent impairment. Adverse drug reactions were more common in the triazolam-treated than the clomethiazole-treated group. The authors conclude that their data: "gives further support to the view that clomethiazole is, at present, the hypnotic drug of choice for use in this age group."

Cognitive-behavioral therapy

Cognitive-behavioral therapy is the most widely-used of psychological treatments for insomnia. About three-quarters of patients benefit. However, the elderly may be less likely to respond. Sivertsen and his colleagues [31] in Norway randomly allocated 44 elderly insomniacs to CBT (N = 16), the hypnotic medication zopiclone 7.5 mg (N = 16), or placebo (N = 12) for 6 weeks. Participants were followed-up for 6 months. Outcome variables included PSG data and sleep diaries. CBT generally was associated with better outcome than zopiclone. Indeed, zopiclone was largely ineffective, hardly separating from placebo. For example, sleep efficiency improved with CBT from 81.4% to 88.9% at 6 weeks and 90.1% at follow-up. Zopiclone was associated with no improvement, and was no different from placebo. Surprisingly, data for time to sleep onset were not presented, and this is the variable on which zopiclone generally shows significant statistical and clinical effects.

Three treatments – cognitive-behavioral therapy, temazepam (7.5–30 mg/night), and their combination – were compared with placebo in 78 insomniacs aged 55 years or more [32]. Participants kept sleep diaries for 2 weeks before, during the 8 weeks of treatment, and after treatment. Polysomnography over 3 consecutive nights was performed before and at the end of treatment. The main outcome variables were time awake after sleep onset and sleep efficiency. All three treatments were more effective than placebo. The combined approach showed a trend to being the most effective. The advantage of CBT was that clinical gains were retained at follow-up whereas the efficacy of the temazepam alone did not. Long-term outcome was less consistent. Subjects were more stratified with the behavioral approach.

The Glass *et al*. meta-analyses [1]

Returning now to these meta-analyses, the authors searched several standard databases from 1966 to 2003, and asked the manufacturers for unpublished studies. Double-blind, placebo- or comparator-controlled studies with random allocation to treatment were considered. Participants who met predetermined diagnostic criteria for insomnia with a mean age in the group of at least 60 were considered. Thus, these were "older" and not necessarily "elderly" subjects. Barbiturates and chloral derivatives were excluded "as these are not recommended for elderly people."

Benefits were quantified by the participants' perceived change in sleep – sleep quality, total sleep time, sleep onset or ease of getting to sleep, and number of awakenings during the night.

Adverse events were categorized as cognitive (memory loss, confusion) and psychomotor (dizziness, loss of balance, and morning hangover effects).

Of 120 studies identified only 20 met the criteria and had usable subjective data. A further four had usable adverse data. In terms of sleep quality, number needed to treat (NNT) with a sedative in order for one to improve significantly was 13. On a 7-point scale this was equivalent to only a 0.14 point difference between sedative and placebo. The increase in total sleep time was about 25 minutes, and the number of awakenings per night was decreased by 0.63.

With respect to adverse events, the number needed to harm (NNH) for sedatives, compared to placebo, was 6. The most common adverse events were drowsiness/fatigue, headache, and nightmares. Cognitive impairment was significantly more common; so was psychomotor impairment but the difference did not reach significance. Seven of the adverse events were designated serious, and comprised six falls and a motor vehicle accident. Morning-after performance was significantly impaired.

The paper contains plots of the effect size of each individual study. Overall, the effect size averaged 0.14 (0.05 to 0.23). For benzodiazepine studies only, the mean value was 0.37 (0.01 to 0.73). (A small effect size is about 0.2.)

The ratio of NNH to NNT is around 2, indicating that an adverse event is twice as likely as even a modestly enhanced quality of sleep.

The authors then review other meta-analyses of effect sizes for total sleep time and sleep quality. Across all ages, effect sizes seemed appreciably greater than for the elderly alone. Similar analyses for adverse events suggested that the elderly are more affected than younger subjects.

The authors conclude that the improvement in sleep variables following the use of sedative hypnotics, although significant statistically, show a small effect size: "…clinical benefits may be modest at best. The added risk of an adverse event may not justify these benefits, particularly in a high-risk elderly population." Non-pharmacological therapies such as CBT may be preferable.

Adverse drug reactions

Annemiek Vermeeren [33] reviewed in minute and critical detail the residual effects of hypnotics, and included 144 references. These mostly referred to studies across all age ranges or to non-elderly subjects. Among her observations is the variability in quality of the studies, particularly those conducted 20 or so years ago: numerous drugs and doses are involved; elimination half-lives across drugs range from 1 to 75 hours; and outcome variables are not standardized, nor are the times of evaluation.

All reviews agree that compounds with long half-lives tend to show more frequent and more severe residual effects than shorter-acting compounds. This seems self-apparent but it depends on efficacy across the compounds to be roughly equivalent. Thus, a long-acting "weak" drug might show fewer residual effects than a shorter-acting "strong" compound. Despite this, evidence points to residual effects becoming less apparent with repeated dosing.

With respect to the focus of this chapter – the elderly – the greatest debate has revolved around falls and hip fractures. The average annual incidence of falls is 36% in community-dwelling elderly patients. Falls are a predominant cause of injuries in the elderly and predict strongly subsequent placements in a nursing home. The use of BZDras is a consistent risk factor for falls and hip fractures in both clinical and community settings. Overall, the risks of hip fracture in the elderly are increased by 50 to 110% in those taking benzodiazepines. Compounds with long half-lives are associated with a higher risk of falls and fractures than those with shorter half-lives. The risks tend to fall away with continued use, particularly of the long-acting drugs.

Time of day is important. Shorter half-life drugs are actually associated with an increased risk of falls during night-time hours. This is highly relevant as it is the norm for even the healthy elderly to rise at least once at night. Dosage is an important factor.

A further factor is polypharmacy. The elderly are more likely than younger people to be taking other medication, either regularly or on an "as-needed" basis. The highest risk of falling is with a combination of a sedative and an antipsychotic drug.

The use of low doses of hypnotics has been cogently argued with special reference to the elderly [34]. However, data are scant and further studies focusing on the elderly are greatly needed.

It is difficult to come to clear-cut conclusions for a host of reasons. Among these are the problems of equating drugs, dosages, time of administration, variations in metabolism polypharmacy and in particular contemporaneous physical illness or general frailty. It is problematic for all the adverse drug reactions (ADR) risks to be combined to come up with an

overall figure. Obviously, a fall with a small bruise is a very different matter from a shattered hip. A major drug reaction with liver damage does not compare with a little heightened sedation.

The usage of various hypnotics varies greatly so that fine detail of risks across drugs is lacking. Prescribing practices change. In the UK zopiclone is supplanting temazepam.

Long-term use and dependence

Prescribing patterns for many countries suggest that the duration of usage rises with age. Some recent data from the UK show that the likelihood of long-term treatment with hypnotics is particularly common and prolonged in insomniacs over the age of 80 (Donoghue and Lader, personal communication). In 2005, only 4.1% of patients up to the age of 30 received more than 12 weeks treatment; for the over-80s the corresponding figure was 40.9%. The figures for zopiclone are similar.

These types of data raise important issues about rebound, dependence, and withdrawal. Tolerance and rebound are particular problems with rapidly eliminated hypnotics [35]. Our knowledge about hypnotic dependence in the elderly is rudimentary but it would seem likely that a substantial proportion of the elderly population using BDZra hypnotics are physically, if not psychologically, dependent on these drugs [36, 37]. The implication is that they would encounter major problems if they tried to discontinue. Are they likely to keep taking these ineffectual drugs for the rest of their lives?

A further concern is that as they age, the elderly become susceptible to the adverse effects of these drugs, in particular the cognitive effects. Memory loss is the most worrying, and there are anecdotal accounts of aged patients being written off as demented, only to recover their wits when their psychotropic medication is discontinued. Hypnotics are the main offenders.

A MEDLINE search covered all options for the treatment of insomnia in the elderly [38]. The author concluded that chronic insomnia occurs more often among the elderly than in younger individuals. There is a paucity of data for the long-term use of sedative-hypnotics for insomnia. Concerns include potential adverse effects including cognitive impairment and anterograde amnesia, daytime (residual) sedation, and motor incoordination. More serious ADRs include road traffic accidents and falls. Both the effectiveness and safety of long-term hypnotic use remain to be established.

Rather different conclusions were reached by Dolder *et al*. [39]. They also carried out a MEDLINE search but provide only a general overview. They include the benzodiazepine receptor agonists zolpidem, zaleplon, zopiclone and eszopiclone, and the melatonin agonist ramelteon. They noted that these drugs were most efficacious at shortening sleep latency and sleep quality, and least effective at prolonging total sleep time. All of them seemed to be well tolerated. Only one study detected any rebound with zolpidem on discontinuation. The possibility that tolerance may occur cannot be excluded; cognitive and psychomotor effects are also a possibility. The conclusions while guarded are optimistic.

Conclusions

An independent review, under the aegis of the UK Consumers' Association examined the role of hypnotic drugs [40]. It noted that elderly patients are especially vulnerable to over-sedation because they metabolize drugs more slowly, are more susceptible to CNS depression, and are more likely to be on potentially interacting drugs. These drugs may contribute to falls and fractures in the elderly. Even small doses can cause acute confusional states, night-time wandering, and, occasionally, paradoxical excitement. Treatment-related impairment of memory and cognitive function may be wrongly diagnosed as features of dementia. The overview recommends: "However, in elderly people, it is safer to avoid hypnotics altogether, wherever possible."

This appears to be closer to the consensus view in countries with conservative prescribing practices such as the UK and Australia. In other countries, hypnotic medication in the elderly is not regarded with as much disapproval. The availability of safer hypnotics, and those working by a non-BZDra mechanism, would help to alleviate this unease.

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Part 4
Chapter
35

Treatment of Sleep Disorders in the Elderly

Use of psychotropic drugs in the elderly: effects on sleep architecture

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Introduction

While people aged 65 and over represent only 12%, 16%, and 21% of the general population in North America, Europe, and Japan, respectively [1, 2], they represent a disproportionate part of medication consumption [3, 4, 5, 6]. Among medical prescriptions, psychotropic drugs are the most prescribed in the elderly after cardiovascular medications [3, 7, 8, 9, 10]. Several factors may explain the high rate of psychotropic prescription in the elderly: presence of neuropsychiatric disorders (including depression and dementia), insomnia, chronic disease, psychological distress, and negative perception of health [6, 10, 11, 12, 13]. Older women and those living in special housing are more likely to take psychotropic drugs than men or old people living at home [6, 11].

The high prevalence of psychotropic use in the elderly can be expressed in two ways. First, there is an increased prevalence with age. Indeed, an increased prevalence of psychotropic medication use with age was consistently reported in North America [12, 14, 15] and Europe [5, 16]. Globally, the consumption of psychotropic drugs significantly increases in the age range 40–59 years compared to younger subjects and continues to progress although slower in older people around 60–65 to 75, with another increment step in very old people (>80 years) mainly due to an increase in prescription of sedatives/hypnotic/anxiolytic (SHA) drugs [9, 11, 14, 15, 16, 17, 18]. In two recent surveys of older adults with and without psychiatric disorders conducted in Canada and the USA [14, 15], the prevalence of SHA intake was 1.5- to 2-fold higher in people aged 60–65 and over than in subjects between 40 and 64 and about 7 times higher than in younger adults. Thus, older subjects in good health (aged 65 and over) were 7.5-fold more likely to use SHA drugs than younger subjects [12]. The use of the other main classes of psychotropics (antidepressants, antipsychotics, and mood stabilizers) remains relatively stable from age 40 years to 60–74 years but a further increased use of antipsychotics and antidepressants is observed in subjects over 74 years [9, 12].

Second, the prevalence of the global consumption of psychotropic drugs has increased during the last decade for the same age range of older people [6, 19]. However, disparities exist across the different classes of psychotropic drugs. The highest rate of consumption in the elderly is found for the SHAs, followed by antidepressants and antipsychotics [6, 9, 17, 19]. Among the SHAs, the benzodiazepines are the most prescribed [12, 15, 18] although their use tends to stabilize or even decline in the last two decades in both institutionalized [20] and home-dwelling subjects [9, 21]. In the same period, the use of the new generation of antidepressants and non-benzodiazepine hypnotics has increased but remains less common than benzodiazepines [9, 20, 21, 22, 23]. The major indications for SHAs in elderly patients are anxiety and sleep disorders, with insomnia being highly prevalent in people aged 65 and over [24, 25]. SHAs are also largely prescribed in mood disorders, often in combination with antidepressants, to alleviate co-morbid symptoms of depression such as anxiety, agitation, and insomnia [6, 15, 26]. Surprisingly, prescription of SHAs is not uncommon in older people with no lifetime disorder [15, 27]. For example, around 15% of Spanish elderly without nervous, depressive, or sleep disorders were prescribed SHAs in 2003 [6].

Despite the fact that psychotropic drugs are widely used in the elderly, little is known about their effects on sleep architecture. This could be of importance since there is emerging evidence that the different hallmarks that characterize sleep architecture, such as spindles, delta waves, or rapid eye movements (REM), are involved in brain restorative processes including memory consolidation [28, 29, 30]. There are also preliminary data suggesting that delta activities in the sleep EEG of elderly healthy subjects may reflect their waking performance on neuropsychological tests [31, 32]. Accordingly, in the present section, the effects on

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sleep architecture of psychotropic drugs will be described. This review will discuss the effects of drugs prescribed as hypnotics or used as hypnotics for their sedative potency as well as the effects of those prescribed for common neuropsychiatric conditions, such as depression and dementia, and that have unintended effects on sleep.

Aging and sleep architecture

Normal sleep follows a predictable pattern called sleep architecture consisting of a well-described progression through several stages. Sleep is normally initiated by non-REM sleep and progresses into rapid eye movement (REM) sleep. A normal night comprises repetitive REM to non-REM cycles, each lasting about 90 minutes. From a physiological point of view, the distinction between sleep versus wakefulness is attributed to the synchronization and desynchronization of thalamo-cortical circuits [33, 34]. Wake-like or "desynchronized" (low amplitude and high frequency) EEG activity with clusters of rapid eye movements and a very low level of muscle tone characterize REM sleep. Non-REM sleep includes all sleep except REM sleep and is by convention divided into three stages that correspond to the progressive increase in depth of sleep from stage 1, to stage 2, to stage 3–4 slow wave sleep (SWS). Thalamically generated spindles (burst of 11–15 Hz activities) and K-complexes (a sharp negative wave followed by a large positive wave) characterize light non-REM sleep stage 2 and as sleep deepens to SWS, there is a progressive dominance of "synchronized" EEG activity (low voltage, high amplitude delta or slow wave activity).

Sleep architecture undergoes significant changes across the lifespan. The Ohayon *et al.* [35] meta-analysis that compared sleep EEG parameters of healthy individuals, from childhood to old age, indicates age-related changes in most sleep continuity and architecture parameters. The most striking normal age-related change is perhaps the reduction in SWS, with women appearing to maintain SWS later in their lifespan than men. Alteration of the homeostatic aspects of sleep could account for the lower SWS propensity observed in this age group, as well as for the increase of sleep fragmentation and the lower sleep efficiency. Moreover, studies using forced desynchrony or constant routine protocols have shown that the typical earlier bedtimes and wake-up times demonstrated by older subjects are primarily related to a weakening of homeostatic processes rather than to changes in the circadian timing system [36, 37, 38].

In contrast to SWS, stage 1 and stage 2 non-REM sleep tend to increase with age [35, 39]. However, sleep spindle activity was found decreased in older healthy subjects [40]. REM sleep tends to be somewhat more preserved and only a modest decline is observed with age. Some studies have found age differences in the duration of REM sleep latency, a finding that may reflect changes in the proportion of the first non-REM period occupied by SWS [41]. A lower occurrence of rapid eye movement has been observed in the REM sleep of older healthy subjects [42].

Effects of psychotropic drugs on sleep architecture

Several neurotransmitter systems are implicated in sleep–wake regulation mechanisms and it is no wonder that, in addition to drugs prescribed as hypnotic agents, numerous other prescription drugs acting in the central nervous system have the potential to affect sleep architecture. In the present section, the effects on sleep EEG of drugs classified as sedatives or hypnotics will be described as well as those of antidepressant and antidementia drugs. It is worth mentioning that, apart from the more recent hypnotic compounds, there is a paucity of well-controlled studies that investigate the sleep EEG effects of psychotropic drugs in the elderly.

Hypnotic drugs acting through $GABA_A$ receptors

Drugs acting on the benzodiazepine site of the $GABA_A$ receptor are the most commonly prescribed drugs for the pharmacological treatment of insomnia. Some of these drugs like triazolam, estazolam, flurazepam, lormetazepam, and temazepam have a benzodiazepine chemical structure and others (such as zolpidem and zopiclone) do not. This group of drugs, also known as positive $GABA_A$ modulators, binds to a specific recognition site on the $GABA_A$ receptor complex, resulting in the facilitation of GABA inhibition and the enhancement of the negatively charged chloride ions flow. $GABA_A$ receptors are pentameric structures composed of different subunits (e.g. α_{1-6}, β_{1-3}, γ_{1-3}) that are differently expressed throughout the central nervous system. Benzodiazepines are known to bind indistinctly to most $GABA_A$ receptor subtypes, while non-benzodiazepine $GABA_A$ modulators such as zolpidem,

zaleplon, and indiplon have a much higher affinity for the receptors containing an α_1 subunit, i.e. α_1-$GABA_A$ receptor [43].

Knock-out studies in mice have shown that α_1-$GABA_A$ receptors may mediate sedation effects of benzodiazepine and non-benzodiazepine $GABA_A$ modulators [44], suggesting that the hypnotic effect of this group of drugs is induced through the occupancy of a recognition site located on these receptors. Consistent with this hypothesis, it has been shown that neurons belonging to the tuberomammillary nucleus (TMN), one of the key wake-promoting structures [45], contain $GABA_A$ α_1 subunits [46]. Moreover, CNS c-Fos expression studies performed after systemic administration of drugs acting on the $GABA_A$ receptor benzodiazepine site indicate that these drugs consistently and completely suppressed c-Fos expression in TMN neurons [47].

Human studies indicate that the pharmacological action of GABAergic drugs acting on the benzodiazepine site include a shortening of sleep latency, an improvement of sleep maintenance, an increase of non-REM sleep, and a reduction of REM sleep. Spectral analysis of the sleep EEG during non-REM sleep shows that these drugs increase spindle frequency activity (12–15 Hz), the hallmark of stage 2 sleep, while tending to suppress delta activity (0.5–4 Hz), which characterize SWS [48]. Period-amplitude analyses indicate that the decreased delta activity resulted mainly from a decrease in wave amplitude, while, in contrast, the increased spindle frequency activity was produced by increased wave incidence [49]. Only a few studies on the effects of GABAergic drugs on sleep architecture of elderly subjects have been published. These studies were conducted in heterogeneous groups of subjects and according to various kinds of design. Consequently, results are not always comparable to those obtained in younger subjects.

Benzodiazepines

Early polysomnographic studies conducted with benzodiazepines in elderly subjects generally corroborate results obtained in young or middle-aged subjects. These studies were performed in elderly insomniacs [50, 51, 52, 53, 54, 55, 56] and one of these concerns insomniac patients with chronic obstructive pulmonary disease [57]. Most of these studies were placebo-controlled with a parallel [51, 56] or a single-blind cross-over design [50, 52, 54, 55]; only two studies used a double-blind cross-over design [53, 57]. Short-term drug administration (for 3–7 consecutive nights) was generally studied although there was one single administration study [57]. Results of these earlier studies are discussed below as well as those obtained from more recent investigations using a benzodiazepine hypnotic drug as an active comparator of new non-benzodiazepine compounds.

As a general rule, results replicate those obtained in young or middle-aged subjects. Thus, benzodiazepine administration in elderly insomniacs had sleep-inducing properties either by shortening sleep onset latency or by improving wake after sleep onset and thereby increases total sleep time. For instance, total sleep time increased with flurazepam (15 mg) [50, 51], nitrazepam (5 mg) [54], lormetazepam (0.5 mg) [52], triazolam (0.125 mg [53] or 0.250 mg [51, 57]), and quazepam (15 mg) [56]. These effects were sustained after a more prolonged drug administration (i.e. 2 weeks for lormetazepam 0.5 mg [52] and 4 weeks for estazolam 1 mg [55]). In general, non-REM stage 2 sleep was found to be enhanced (brotizolam 0.25 mg [58] or flurazepam 15 mg [50]), sometimes at the expense of SWS (nitrazepam 5 mg [54]), but some studies found SWS enhancement after benzodiazepine intake. REM sleep was usually found unchanged (triazolam 0.125 mg [53]) or decreased (flurazepam 15 mg [50] and nitrazepam 5 mg [54]).

Zolpidem

Four polysomnographic studies used different designs to investigate the effects of zolpidem in various samples of elderly insomniac subjects (psychiatric inpatients, patients with chronic obstructive pulmonary disease, and patients with non-organic or primary insomnia). Another study investigated healthy non-insomniac elderly subjects.

Scharf *et al.* [59] demonstrated the sleep-inducing effect of four different doses of zolpidem (5 mg, 10 mg, 15 mg, and 20 mg) in 30 healthy subjects with a mean age of 67.8 years (range 60–79 years); the study was placebo-controlled and cross-over with an incomplete block design such as half of the sample were randomized to a placebo/zolpidem 5 mg/zolpidem 15 mg sequence and the other half to a placebo/zolpidem 10 mg/zolpidem 20 mg sequence. Results showed that all doses produce a significant improvement in sleep latency and in wake time during sleep. Regarding sleep architecture, REM sleep was slightly decreased with zolpidem 10 mg and 20 mg, stage 2 was increased with

zolpidem 20 mg, while SWS was left unchanged with the four doses.

Kummer *et al.* [60] reported the results of an open long-term trial on the effect of zolpidem (20 mg) in chronic psychiatric inpatients (N=14; age 67.8 ±2.2 years). Polysomnographic assessments during treatment were performed on a regular basis (after 1, 3, and 6 months) and compared to a baseline recording obtained after a 7-day placebo run-in period. Statistically significant improvements in total sleep time, sleep efficiency, and REM sleep percentage were observed after 1 month of treatment, all of which were maintained after 6 months of treatment. Stage 2 was found significantly increased only after 6 months of treatment, and zolpidem affected neither sleep onset latency nor SWS in this sample of patients. These results are difficult to interpret in light of other zolpidem studies because of the high dosage used in the study and the heterogeneity of the sample (i.e. patients with chronic psychotic conditions or organic mental disorder) as well as the concomitant treatments (mostly chlorprothixene, haloperidol, or maprotiline).

Steens *et al.* [57] compared in a group of 24 insomniac patients with chronic obstructive pulmonary disease (age 58.2 ±5.5 years) the effects of a single administration of zolpidem (5 mg and 10 mg) to those of triazolam (0.250 mg) using a double-blind placebo-controlled cross-over design. The results showed that total sleep time and wake time during the sleep period improved compared to placebo and that sleep onset was shortened by all three drug conditions. Compared to placebo, SWS was increased with zolpidem, but the placebo to drug differences only reached significance for the zolpidem 5 mg dose. No effect of zolpidem was observed on stage 2 or on REM sleep.

Uchimura *et al.* [58] investigated the effects of zolpidem (10 mg) versus brotizolam (0.25 mg) in 14 non-organic insomniac patients (age 54.9 ±8.9 years) using a double-blind cross-over design. The drug was administered for three consecutive nights that were preceded by an adaptation night and two placebo nights. Unfortunately, the drug effects on sleep onset latency, total sleep time, and wake after sleep onset were not reported. Results show that, for the whole-night recording, zolpidem did not induce significant alteration in sleep architecture; however, when the analyses were restricted to the 150-minute period following *T*max, zolpidem showed a significant stage 2 sleep-inducing effect during the 1st and the 2nd treatment nights. It is noteworthy that the effects of zolpidem are significantly different from those of brotizolam on SWS (greater with zolpidem during the *T*max periods of the 1st and the 3rd nights) and on REM sleep (lower with zolpidem during the 3rd whole-night recording).

The recent study by Walsh *et al.* [61] documented the effects of a 3-week treatment of an extended-release formulation of zolpidem (6.25 mg) in 205 primary insomniac patients (age 70.2 ±4.5 years). The drug was administered in a double-blind placebo-controlled parallel group design and polysomnographic recordings were planned on nights 1 and 2 and 15 and 16 of the treatment period. Compared to pretreatment baseline assessments, a significantly greater improvement of latency to persistent sleep and of wake after sleep onset were observed with zolpidem extended release than with placebo on both nights 1/2 and nights 15/16. Some slight changes in the duration of stage 2 (higher with zolpidem), SWS (lower with zolpidem), and REM sleep (lower with zolpidem) were observed, but are of uncertain statistical significance since only descriptive statistics were performed.

To summarize, these four studies confirmed the zolpidem sleep-inducing properties (both on sleep initiation and sleep maintenance parameters) in older insomniac subjects; sleep architecture was inconsistently affected by zolpidem with some studies showing an enhancement of stage 2 sleep or of SWS but others not. REM sleep was generally found unchanged except in psychiatric inpatients, an effect that could relate to the concomitant treatment of these patients. These results are in general accordance with those observed in young and middle-aged insomniacs where zolpidem has shown sleep-inducing effects with inconstant alterations of stage 2, of SWS, and of REM sleep. As discussed by Kanno *et al.* [62] discrepant results on sleep architecture could relate to insufficient sample size in certain studies, repeated versus single administration, as well as time lag between drug administration and recording starting time.

Zopiclone

Zopiclone has a benzodiazepine-like pharmacological profile, and shows no selectivity for the different subtypes of $GABA_A$ receptors [43]. However, its binding site has been reported to be distinct from that of the classical benzodiazepines [63]. Three studies investigated the effects of either zopiclone [64, 65] or of eszopiclone [66], the active stereoisomer of zopiclone, on the polysomnographic recordings of elderly insomniac

patients and one study [67] investigated the effects of zopiclone in healthy elderly subjects.

Hemmeter *et al.* [67] performed a three-period cross-over study comparing the effect of a single administration of either zopiclone (7.5 mg), temazepam (20 mg), or placebo in a group of 12 elderly healthy subjects aged 65.9 ±3.6 years. Results show a significant effect of both drugs on sleep onset latency and wake after sleep onset, although the effect of zopiclone was superior. In contrast to temazepam, zopiclone demonstrated some non-REM sleep-inducing effect (i.e. it increased stages 2 and 4). Regarding REM sleep, both drugs did not affect REM latency or REM sleep time but they significantly reduced REM density. Arguing on the fact that the administration of zopiclone, but not of temazepam, was able to reproduce the drug effects obtained in younger or middle-aged subjects, the authors suggested that age-related differences in $GABA_A$ receptor subtype function could account for the difference in sleep architecture alteration [67]. Indeed, suppression of REM and SWS is generally observed in younger subjects after application of temazepam or other classical benzodiazepines [68, 69, 70]. On the contrary, the zopiclone effects observed in this sample of elderly healthy subjects confirm the results of previous studies on a sample of young and middle-aged healthy subjects, including the effect on SWS [71, 72, 73, 74]. The authors also pointed out the potential deleterious effect of the two drugs on REM density and suggest that it could account for the impairment of sleep-related memory consolidation observed with the two drugs [67]. Indeed, a procedural memory task only improved after placebo intake and not after the administration of both active substances.

In a double-blind parallel group study, Mouret *et al.* [64] compared the effects of a short-term (first 3 treatment nights) and a medium-term (last 3 nights of a 2-week treatment) administration of zopiclone (7.5 mg) in five elderly insomniacs (age 72.2 ±13.8 years) to those obtained with triazolam (0.25 mg) in five different elderly insomniacs (age 64 ±6.1 years). Comparisons with baseline values obtained during a 3-night placebo run-in period indicated that zopiclone, but not triazolam, significantly enhances SWS both after short- and medium-term administration. In that study zopiclone also increased total sleep time and stage 2 (short- and medium-term administration) and REM sleep (only short-term administration) but did not affect sleep onset latency.

However, SWS enhancement after zopiclone was not replicated in a double-blind parallel designed randomized trial comparing the effects of a 6-week treatment of cognitive behavioral therapy versus zopiclone (7.5 mg) or placebo in a group of 46 insomniac patients aged 60.8 ± 5.4 years using non-attended home-based polysomnography [65]. Neither total sleep time nor total wake time was found to be affected by zopiclone. Unfortunately, the effects on sleep onset latency, on duration of stage 2, and on duration of REM sleep were not reported. The authors suggested that a tolerance to the effect of zopiclone could account for the results.

In a 2-week parallel-group designed study evaluating eszopiclone (2 mg), McCall *et al.* [66] showed in a large sample of elderly insomniacs (128 patients aged 70.7 ±4.9 years in the placebo group and 136 patients aged 71.5 ±5.2 years in the eszopiclone group) a beneficial treatment effect for sleep onset, sleep maintenance, and sleep duration. Results from the polysomnographic recordings obtained during the first two dosing nights showed that, compared to placebo, eszopiclone significantly improved latency to persistent sleep, total sleep time, and wake after sleep onset. Among the different stages, only stage 2 was significantly increased with eszopiclone and no significant effect could be evidenced on SWS and on REM sleep.

To sum up, results of the four zopiclone/eszopiclone studies performed in elderly subjects generally demonstrated sleep maintenance properties, although one study showed negative results [65]. Improvement of sleep initiation was reported in two studies [66, 67]. The three studies reporting on the drug effect on stage 2 sleep showed that zopiclone or eszopiclone promote this sleep stage. Results on SWS were discrepant: the two studies showing negative results were the 6-week administration trial [65] and the eszopiclone study [66]. No consistent effects were found on REM sleep that was generally found unchanged with zopiclone.

Others GABAergic drugs

Over the last decade, GABA-mediated inhibitory transmission through receptors located outside the synapses that are activated by the extracellular GABA levels has triggered a great deal of interest [75]. This form of inhibition is generally referred to as GABAergic tonic inhibition in contrast to GABAergic phasic inhibition mediated through $GABA_A$ receptors situated at the synapse. It is thought that neuronal excitability is controlled by these extrasynaptic receptors rather

than by phasically active channels at the synapse [75, 76] and it has been suggested that tonic inhibition may be the preferred target for new sedative-hypnotic drugs [77].

$GABA_A$ receptors containing δ subunits (δ-$GABA_A$ receptors) have been shown to mediate tonic inhibition in various brain regions [75]. Interestingly, δ-$GABA_A$ receptors are observed on thalamic relay neurons [78] that play a key role in the generation of spindles and delta waves [34]. These receptors are devoid of the benzodiazepine recognition site and are sensitive to gaboxadol, a $GABA_A$ agonist that has been in development for the treatment of insomnia [79]. In contrast to α_1-$GABA_A$ modulators, gaboxadol (10–20 mg) clearly promotes delta/theta activities and decreases spindle frequency activities [80, 81]. These effects on sleep microstructure were shown to be reflected by a SWS enhancement and by improvement of sleep onset latency, total sleep time, and wake after sleep onset in a post-nap sleep model of insomnia [82] and in primary insomniacs [83, 84]. Interestingly, gaboxadol did not affect REM sleep parameters (duration and latency). The acute effects of gaboxadol (15 mg) in the elderly were investigated in two small studies each performed on 10 healthy subjects aged 61–78 years [85, 86]. Results show that, on the whole, the effects of gaboxadol were comparable to those observed on younger subjects, excepted for sleep onset latency. The authors [85, 86] stated that, to a large extent, the drug reverses the typical age-related sleep changes; indeed gaboxadol decreases intermittent wakefulness, promotes SWS, and enhances slow frequency activities in the EEG within non-REM sleep, while hardly affecting REM sleep.

Another potential intervention for controlling the amount of the tonic δ-$GABA_A$ transmission is regulating the levels of extracellular GABA; indeed, tonic inhibition is particularly sensitive to the amount of GABA uptake [75]. In this regard, the GABA uptake inhibitor tiagabine, an anti-epileptic agent, shares many pharmacodymanic properties with gaboxadol in terms of sleep effects in aged subjects. In a small sample of healthy subjects (N=10, age 59–78 years), Mathias *et al.* [87] showed in a cross-over double-blind study that a single administration of tiagabine (5 mg) increases sleep efficiency, SWS, and slow wave activity. There were marginal but non-significant improvements in total sleep time and in wake after sleep onset. Sleep onset latency and REM sleep were not affected by tiagabine and, in contrast to gaboxadol, no decrease in spindle frequency activities could be observed after tiagabine. The authors suggested that these differences could be accounted for by the fact that GABA re-uptake inhibition also affects $GABA_B$ neurotransmission. A larger parallel-group study investigating the effects of 3 doses of tiagabine (2, 4, and 8 mg) or placebo on 2 consecutive nights in 24 healthy elderly subjects (aged 68 ±2 years,) replicated these results and extended it to wake after sleep onset and total sleep time, which were found significantly improved with the two highest tiagabine doses [88]. However, these results were not replicated in elderly insomniacs [89]. In this large parallel-group study that investigated the effects of 4 doses of tiagabine (2, 4, 6, and 8 mg) or placebo on 2 consecutive nights in 207 insomniacs aged 65–84 years, it was shown that tiagabine did not significantly affect total sleep time, wake after sleep onset, and latency to persistent sleep although the three highest doses increased SWS. A significant reduction of time spent in REM sleep was also observed with the two highest doses. In order to reach the significant improvement in sleep maintenance observed in healthy subjects, higher dosages of tiagabine are probably needed in insomniac patients; indeed, in younger insomniac patients, only tiagabine 16 mg was able to lower wake after sleep onset but tolerance issues and next-day residual effects appeared with doses higher than 8 mg [90].

Other hypnotic drugs

The hypnotic drug ramelteon, a potent agonist at the two subtypes of the high-affinity melatonin receptor (MT1 and MT2), acts through a non-GABAergic mechanism to induce sleep. Sleep effects of ramelteon in the elderly were investigated in a cross-over trial in which ramelteon (4 mg and 8 mg) and placebo were administered during 2 consecutive nights in 100 primary insomniacs (age 65–83 years) [91]. Results show that, compared to placebo, ramelteon 4 mg and 8 mg shortened latency to persistent sleep and increased total sleep time without affecting wake after sleep onset. Ramelteon did not alter REM sleep but the two doses significantly decreased SWS and the 8 mg dose increased stage 2. These findings were comparable to results of studies performed in younger insomniac patients [92, 93].

Antidepressant drugs

In 1982, McCarley posited that an imbalance between aminergic and cholinergic influences underlie REM

sleep disinhibition in depressive disorder [94]. Conventional supports for the imbalance theory are based on the fact that the REM sleep suppressant effect of antidepressant drugs might be attributed to facilitation of noradrenergic and/or serotoninergic function or to cholinergic blockade. In some cases, as with most tricyclic antidepressants, all three mechanisms may be involved. Antidepressant drugs devoid of clear-cut REM suppressant effects (i.e., amineptine, bupropion, mirtazapine, nefazodone, tianeptine, trazodone, and trimipramine) share one characteristic: their potency to inhibit noradrenergic or serotoninergic uptake is either absent, doubtful, or moderate [95].

A couple of studies investigated the effects of antidepressant drugs on the sleep architecture of elderly subjects. During the 1990s, the Pittsburgh group reported on the persistent sleep EEG effects of antidepressant drugs and interpersonal psychotherapy in elderly depressed subjects. Patients (60–80 years old, N = 72) were recorded during a 1-year study period with nortriptyline (about 80 ±40 mg) prior to acute treatment, after remission, and 1, 6 and 12 months in the maintenance treatment that consisted of either nortriptyline or placebo. Results showed that nortriptyline persistently decreased REM sleep, increased REM activity, and enhanced the rate of delta wave production in the first non-REM sleep period [96, 97]. No significant effects on sleep initiation or maintenance parameters were observed. These results were in agreement with an earlier 3-year maintenance study by the same group that was performed in younger depressed subjects with another tricyclic antidepressant (imipramine 150–300 mg). The latter study showed stable REM and SWS changes (REM sleep suppression, increased REM activity, and redistribution of SWS in the first part of the night) during the imipramine treatment [98].

The non-tricyclic antidepressant trazodone (150 mg nightly for 3 weeks) also has shown sustained REM sleep-suppressing effects in nine elderly poor sleepers (aged 50–70 years); in contrast to nortriptyline, trazodone induced a clear-cut SWS enhancement, but it did not change total sleep time or sleep onset latency [99]. This sleep EEG profile was comparable to those observed in younger healthy or depressed subjects [100, 101, 102]. Wolf *et al.* [103] compared the effects of a 5-week treatment with fluoxetine (20 mg) or trimipramine (150 mg) in 19 elderly depressed patients (age 61–83 years) using a double-blind parallel group design. Findings were similar to results of other studies performed in samples comprising younger subjects [104, 105, 106, 107, 108]. Trimipramine did not affect REM sleep but was found to increase total sleep time and stage 2 sleep and to reduce wake after sleep onset. In contrast, fluoxetine did not influence these parameters but did suppress REM sleep. The latter study further stresses the fact that no age-related differences could be evidenced on the sleep EEG profile of antidepressant drugs.

Antidementia drugs

Data coming from both preclinical and clinical research indicate that the cholinergic neurotransmission system plays a key role in REM sleep generation. REM "on" cholinergic neurons have been located in the laterodorsal and the pediculopontine tegmental nuclei and are involved in the initiation of cortical desynchronization through excitatory inputs to the thalamus and in the occurrence of muscle atonia and rapid eye movements that characterize REM sleep [109]. A marked decrease in cholinergic activity is believed to contribute to the cognitive decline of patients with Alzheimer's disease [110]. This cholinergic deficit is also reflected in REM sleep characteristics of patients with Alzheimer's disease that often exhibit a lower REM sleep percentage and a slowing of the REM sleep EEG [111]. Acetylcholinesterase inhibitors, currently approved for the treatment of mild to moderate forms of Alzheimer's disease, increase cholinergic transmission by blocking the enzymatic breakdown of acetylcholine and have been shown to increase REM sleep propensity in elderly [112, 113, 114] and younger healthy subjects [115, 116, 117, 118, 119] as well as in patients with Alzheimer's disease [120, 121].

In a more general way, human studies indicate that acute administration of cholinergic agonists increase REM sleep propensity whereas acute administration of cholinergic antagonists produces the opposite effect [122]. Based upon the pharmacological profile of the compounds used to manipulate sleep, it appears that both M1 and M2 muscarinic receptor subtypes are involved in REM sleep regulation: at the present time there is some evidence that M1 receptors mediate REM onset (i.e. REM latency) whereas the maintenance of REM sleep (i.e. time spent in REM sleep) and the number of rapid eye movements (i.e. REM density) are mediated by M2 receptors [119]. Some data suggest age-related differences in the REM sleep effects of cholinergic enhancing agents. For instance, the

anticholinesterase inhibitor rivastigmine and RS-86, a muscarinic M1 receptor agonist, showed a more pronounced REM sleep effect on healthy elderly subjects than on younger ones [113, 117]. Moreover, one study in young healthy subjects failed to find a REM sleep effect of the anticholinesterase inhibitor donepezil [123] and another one found an effect limited to REM sleep latency [118]. It has been proposed that age-associated cholinergic deficit resulting in differences in drug sensitivity could account for these results [112].

Some studies investigated the effects of anticholinesterase inhibitors on the sleep of Alzheimer's disease patients. In a 6-week open study, it was shown that donepezil significantly improved REM sleep percentage, total sleep time, sleep efficiency, and sleep latency while REM latency and non-REM sleep were left unchanged [120]. The REM sleep results were confirmed in a double-blind parallel-group study comprising 35 patients that were randomly allocated to either donepezil or placebo [121]. REM sleep percentage increased significantly after 3 and 6 months of donepezil treatment compared with baseline or placebo. Moreover spectral analysis of the REM sleep EEG indicated that donepezil reduced slow frequencies in the frontal and occipital areas. No effects on REM latency, REM density, sleep latency, total sleep time, non-REM sleep, or on sleep efficiency could be evidenced [121]. Interestingly, these two studies on Alzheimer's disease found that either baseline pretreatment REM sleep EEG alpha activity [121] or donepezil-induced REM sleep enhancement [120] correlate with treatment-induced cognitive improvement. The latter findings have to be compared with results of two studies in healthy elderly subjects showing improved memory performance associated with enhancement of REM sleep [114, 124].

Conclusions

Although there is a wide consumption of psychotropic drugs in the elderly, little is known about their effects on sleep architecture. This is a matter of importance since there is a growing evidence [30, 125] that sleep architecture, and in particular the physiological REM/non REM alternation, play a key role in brain plasticity and therefore in brain restorative processes that are supposed to decrease with age. The most well-documented effects of psychotropic drugs on sleep architecture in the elderly are those of hypnotic drugs. Results of these studies indicate that, grossly speaking, the effects of hypnotic drugs on sleep architecture of elderly subjects do not markedly differ from those observed in younger subjects. This also seems true for tricyclic antidepressants, but the effects of other classes of antidepressant on the sleep architecture are to a larger extent unknown. Finally, some (but not all) studies with anticholinesterase inhibitors tend to indicate an age-related effect on sleep architecture, particularly on REM sleep parameters.

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Part 4
Chapter
36

Treatment of sleep disorders in the elderly

Non-pharmacological treatment of insomnia in the elderly: cognitive behavioral therapies

Philip R. Gehrman and Nalaka Sudheera Gooneratne

Background

Insomnia is the most prevalent sleep disorder in older adults, as described in previous chapters. Pharmacotherapy has traditionally been the first-line treatment for insomnia despite the potential risks, particularly in older adults, such as increased daytime sedation and risk of falls [1]. Pharmacotherapy also does not address the underlying mechanisms that perpetuate insomnia over time, necessitating long-term pharmacotherapy for most individuals [2]. Non-pharmacological treatment has been increasingly recognized as the preferred approach and data continue to support its efficacy.

The dominant non-pharmacological treatment is cognitive behavioral therapy for insomnia (CBT-I). CBT-I is based on both general principles of cognitive behavioral therapy and current models of sleep/wake regulation. Cognitive behavioral therapy is predicated on the concept that emotions, thoughts (cognitions), and behavior are all reciprocally related such that changes in one domain produce changes in the other domains. Historically, psychological therapies have attempted to effect change in emotions directly. Generally this has proven to be a difficult task. The behavioral school of thought emphasized the primacy of observable behavior and the ability of behavioral change to lead to changes in thoughts and emotions. Similarly, Beck was one of the first to recognize that changing patterns of thinking can produce changes in emotion and behavior, and became the father of the cognitive therapy revolution [3]. Cognitive behavioral therapy (CBT) represents a merger of these approaches, utilizing a combination of behavioral and cognitive strategies to effect change across domains of functioning. There is a substantial body of research demonstrating that CBT is an efficacious treatment for a wide range of psychological problems ranging from depression and anxiety, with more recent research confirming the efficacy of this approach for treating more difficult conditions such as schizophrenia [4]. Over the past few decades the application of cognitive behavioral principles to the treatment of insomnia in both younger and older adults has generated a large body of scholarly work.

CBT-I also draws on principles of sleep/wake regulation. Borbely and colleagues were the first to propose the 2-process model of sleep regulation in which sleep and wakefulness are primarily regulated by: (1) a homeostatic process that accumulates during waking and is discharged during sleep; and (2) circadian rhythms in sleep propensity by which sleep or wake are promoted during particular portions of the 24-hour day [5]. Several components of CBT-I described below seek to facilitate sleep by maximizing homeostatic drive for sleep and ensuring that both the timing and strength of circadian rhythms are maximized.

The current conceptualization of insomnia and CBT-I is based on Spielman's 3-P model of insomnia [6]. According to this model, depicted in Figure 36.1, there are individual differences in underlying risk for developing insomnia. These *predisposing* factors may include age, genetics, and personality traits. Consistent with diathesis-stress models of mental illness, a stressor of some sort is needed to trigger the initial onset of insomnia, referred to as a *precipitating* factor in this model. A common precipitating factor for insomnia is life stress, with other factors including mental illness (usually depression or anxiety), physical illness (especially those associated with chronic pain), or the effects of a substance. For individuals with a high predisposition to develop insomnia, minor precipitating factors may be sufficient to initiate an episode of insomnia, whereas stronger factors would be necessary in cases of low predisposition. In the majority of cases, resolution of the precipitating event leads to improvement in sleep such that only a transient episode of insomnia occurs. In others, the insomnia is maintained over time by *perpetuating* factors that replace the precipitating factors over time. For example, a patient with insomnia may begin to worry

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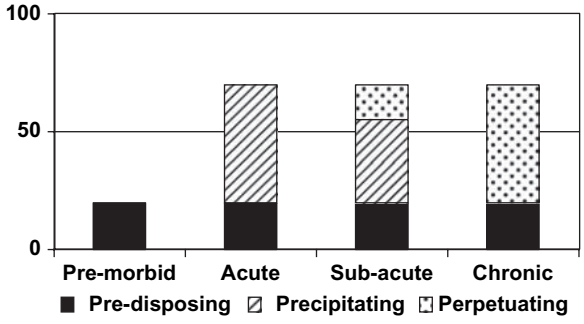

Figure 36.1. Spielman's (3-P) model of insomnia.

about being able to sleep at night such that the worry ends up interfering with sleep. Another perpetuating factor is napping, where an individual naps during the day to make up for lost sleep but then has trouble sleeping the following night because of reduced homeostatic drive for sleep. Perpetuating factors can maintain insomnia for years beyond the resolution of the initial precipitants. Whereas pharmacotherapy seeks to override the perpetuating factors, CBT-I is designed to address these perpetuating factors directly.

Treatment components

CBT-I is comprised of a series of behavioral and cognitive strategies that address the perpetuating factors that have maintained the insomnia, sometimes for many years. Although treatment consists of an integration of each of these strategies they will be discussed separately in the sections below. First, approaches that target changes in behavior will be covered, followed by those that target thought processes.

For all CBT-I approaches, an important component of treatment is maintaining a patient-completed sleep diary or sleep log. Patients should complete at least 1 week (ideally 2 weeks) of sleep diary data prior to starting CBT-I and prior to each treatment visit. Wrist-activity monitors (actigraphy) can also be used [7], although they are not widely available and are not routinely reimbursed by insurance providers.

Behavioral treatment approaches

Sleep hygiene

The most basic behavioral treatment approach is called *sleep hygiene* [8]. It is essentially a collection of guidelines that, when followed, can promote healthy sleep. Many of them represent maladaptive coping strategies that individuals use when they are having trouble sleeping. Paradoxically these strategies can actually serve to perpetuate the insomnia over time.

1. Minimize napping. Many individuals engage in daytime naps in order to manage daytime sleepiness produced by sleep loss. Older adults in particular are much more likely to engage in naps [9] because they may not be as tied to a structured daytime routine following retirement. The daytime sleepiness that prompts napping is a response to increased homeostatic drive, which is reduced by napping. However, this leads to a reduced homeostatic drive at night, which in turn can make it more difficult to initiate and/or maintain sleep. Hence, while it is a reasonable countermeasure to the daytime consequences of insomnia, napping can serve as a perpetuating factor. It may not be necessary to completely eliminate napping, but naps should be kept to a single period of 30 minutes or less.

2. Maintain a regular sleep schedule. For many individuals with insomnia, bedtime and waking time vary considerably from day to day [10]. This may represent a compensatory phenomenon where the individual attempts to "sleep in" to recover after a poor night of sleep. Following a consistent sleep and waking schedule can enhance entrainment of circadian rhythms such that sleep-promoting brain processes can begin to engage in anticipation of bedtime and waking processes can engage in anticipation of waking. It is often easier for patients to maintain a regular bedtime, but they should be encouraged to also keep to a consistent rising time even if this necessitates utilizing an alarm clock. Similarly, weekend schedules should not deviate from weekdays by more than 1 hour, although this may be less of an issue for older compared to younger adults.

3. Ensure that the sleeping environment is sleep-promoting. The bedroom should be comfortable and be free from excessive noise, light, or other sensory stimulation that could negatively impact sleep. There are a number of countermeasures that patients can engage in to minimize these influences such as dark curtains, ear plugs, or white noise machines. Ambient temperature preferences vary across individuals but a cooler room can promote more slow wave sleep compared to a warmer room [11]. Although there is insufficient data for recommending a particular type of mattress, comfort is of course important.

4. Avoid caffeine after lunch. Most patients are unaware of the long half-life of caffeine and do not realize that even small quantities of caffeine later in the day can interfere with sleep even hours later.

Patients should be educated about the various sources of caffeine other than coffee, such as certain teas, chocolates, and sodas. Although many patients can consume caffeine in the morning, some sensitive individuals may need to eliminate caffeine altogether. If baseline caffeine intake is high then a gradual reduction can minimize the potential for withdrawal effects.

5. Similarly, many individuals are not aware of the potential influence of alcohol on sleep. Alcohol is commonly used as a form of self-medication to promote sleep [12]. While the effects of alcohol can promote sleep onset initially, metabolic by-products can interfere with the depth of sleep, reducing sleep quality and contributing to an increased propensity towards awakening after 1–2 hours. Perhaps more seriously, use of alcohol as a coping mechanism for any problem can lead to development of dependence. As with caffeine, a gradual decline in alcohol consumption may be warranted if baseline intake is high.

6. Engage in regular exercise, but not immediately before bed. Regular aerobic exercise has been shown to improve both sleep quality and quantity, as well as increase the amplitude of circadian rhythms [13]. Aerobic exercise increases core body temperature. Given that the nocturnal decline in core body temperature seems to play a permissive role for sleep onset, exercising too late in the day may delay this decline and inhibit sleep. In line with the influence of core body temperature, a warm bath at night may facilitate sleep onset due to the post-bath rapid decline in core temperature.

7. Increase exposure to bright light during the day. Bright light has been shown to be one of the primary zeitgebers, or cues, that regulate circadian rhythmicity. Older adults have been shown to have reduced bright light exposure compared to younger adults, with the situation exacerbated for those in nursing homes [14]. Increasing daytime light exposure can increase the amplitude of circadian rhythms. In fact, bright light therapy has been shown in some studies to improve the sleep and circadian rhythms of older adults as discussed in more detail in other chapters.

8. Add a "wind down" period before bed. As it takes the mind some time to disengage from daytime activities, patients should have a minimum of 30 minutes prior to going to bed during which they are involved in relaxing activities.

This list of sleep hygiene guidelines is by no means comprehensive and other published lists may include a somewhat different set of rules. One of the most important elements of sleep hygiene is that patients learn to appreciate that their daytime activities can influence their sleep at night, even hours later. It is important to note than many people engage in these behaviors yet do not have any difficulty sleeping. In fact, studies have found that individuals with insomnia do not necessarily engage in these behaviors with greater frequency than good sleepers [15]. Poor sleep hygiene habits most likely interact with an individual's risk factors for insomnia such that vulnerable individuals are more sensitive to these behaviors. At the same time, the adoption of good sleep hygiene practices is usually not sufficient on its own to correct an ongoing problem with insomnia. Sleep hygiene therefore is a necessary, but not a sufficient, ingredient of CBT-I. Attempting to adopt all of the above sleep hygiene modifications at one time can be difficult, and some patients may be more compliant with a stepwise implementation.

Stimulus control

One of the main behavioral treatment approaches is stimulus control. Within the behaviorist tradition of psychology, operant conditioning is based on the shaping of behavior by its consequences such that behaviors that are rewarded increase in frequency and those that are punished decrease in frequency. A stimulus can serve as a cue that reinforcement is likely and is referred to as a discriminative stimulus. In the context of sleep, the bed can serve as a discriminative stimulus that serves as a cue that reinforcement (sleep) is likely to occur, thus facilitating the onset of sleep. Oftentimes people engage in non-sleep behaviors in bed such as reading, watching TV, paying bills, etc. before bedtime [12] that weaken the stimulus value of the bed, i.e. the bed does not serve as a cue for sleep and may in fact serve as a stimulus for arousing activities. Stimulus control seeks to establish a new pattern of conditioning by producing a one-to-one correspondence between the bed and sleep [16]. This is accomplished by having patients follow a simple set of rules.

First, they are instructed to avoid sleep-incompatible activities in bed by using the bed only for sleep. Sexual activity is often allowed as the sole exception to this rule. Reading, watching TV, and other activities should occur in other rooms or at least not in bed. Second, patients should only get into bed when they are sleepy. Often people with insomnia will get into bed early in

order to maximize their chances of obtaining sufficient sleep, even if they do not yet feel able to sleep. The lack of sleepiness may be due to insufficient homeostatic drive build-up and/or sleep being attempted at the wrong circadian phase. Getting into bed too early virtually guarantees that sleep onset latency will be long, weakening the stimulus relationship between the bed and sleep. Lastly, and most importantly, is what patients should do if they have difficulty falling asleep. They should be told that, if they are not asleep in 15–20 minutes (based on subjective estimation and not watching the clock) then they should get out of bed, engage in non-arousing activities, and then get back into bed when they feel ready to fall asleep. If another 15–20 minutes passes without sleep onset, they should get out of bed again. The same rule applies if they are awake during the night. Consistently following these guidelines reduces time spent awake in bed, strengthening the stimulus relationship between the bed and sleep.

After the initial operant conditioning rationale for stimulus control, a complementary classical conditioning model was proposed. Classical, or associative, conditioning occurs when two stimuli become temporally paired so that a response initially produced by one of the stimuli can then be produced by the other stimulus. For good sleepers, there is a classically conditioned association between being in bed and sleeping so that just getting into bed can produce the response of feeling sleepy. Individuals with insomnia can have the opposite pattern such that they associate being in bed with wakefulness and hyperarousal. As a result, these patients often report feeling more awake and mentally alert after getting into bed. Stimulus control can modify this response by strengthening the association between being in bed and sleeping. Over time, patients often report that they feel a reduced tendency towards an arousal response upon getting into bed.

Sleep restriction

Patients with insomnia often spend excessive time in bed in order to obtain their desired sleep time. For example, total sleep time may be 6–7 hours per night but this is obtained by spending 10 hours in bed. In this case there is a mismatch between *sleep opportunity* (time in bed) and *sleep ability* (total sleep time) leading to sleep that is inefficient. Sleep restriction as a treatment strategy was created as a way to match sleep opportunity with sleep ability. The first step in sleep restriction is to have the patient monitor their sleep for 1 week using a sleep log in order to determine the average total sleep time per night. Time in bed is then set equal to this average, with a minimum of 5 hours typically used. For example, if an individual is obtaining 6 hours of sleep per night on average, they will now only spend 6 hours in bed. The new sleep schedule is determined by starting with the desired rising time and counting backwards by the time that will be spend in bed.

In the short run, patients end up getting less sleep than they are used to, which is precisely the mechanism through which sleep restriction is proposed to work. Over the course of 2–3 weeks, homeostatic sleep drive accumulates and eventually leads the individual to be asleep for an increasing proportion of their time in bed. This mechanism of action makes sleep restriction a particularly good fit for older adults, since increasing age is associated with a decline in homeostatic drive [17]. Sleep is continually monitored throughout treatment in order to determine average sleep efficiency (percentage of time in bed spent asleep computed by dividing total sleep time by time in bed). Once sleep efficiency reaches 90% on average for a week then the window of sleep opportunity is increased by 15–30 minutes by moving the bedtime earlier. When 90% is achieved on this new schedule, bedtime is again moved 15–30 minutes earlier. If sleep efficiency drops below 80% time in bed is reduced by 15 minutes.

By following these guidelines there is a decrease in time in bed early on, followed by a gradual increase. One way to think about the approach is that the brain is "trained" to sleep efficiently using sleep deprivation, and then given more time to apply this newfound skill. Since sleep restriction involves continuous monitoring of sleep to determine if adjustments to the sleep schedule are needed, there may be frequent patient-provider contact. However most of these contacts are a brief check-in that can be handled over the phone or via email. It is important to be aware of the potential risks of increased sleep deprivation produced by sleep restriction. As noted below (see the section titled "Safety considerations"), these risks need to be managed carefully to maintain patient safety.

It has been suggested that older adults may have difficulty with the rigid schedule of self-imposed sleep deprivation associated with sleep restriction. They are also at greater risk of experiencing falls and other consequences of sleep deprivation. For these reasons, *sleep compression* has been suggested as a milder version of

sleep restriction [18]. Rather than a sudden curtailment of time in bed, sleep compression is more gradual. The mean difference between total sleep time and time in bed is calculated over a week using sleep logs. Time in bed is then restricted by one-fifth of this time difference per week. Further changes are then made in accordance with standard sleep restriction guidelines.

Relaxation therapies

Patients with insomnia usually report physical and/or mental tension at night when trying to sleep. In order to reduce this tension various relaxation strategies can be employed. There is a wide array of relaxation strategies available with no clear advantage of one over another. One that is widely used is progressive muscle relaxation (PMR), which involves having patients systematically tense and relaxes each of the major muscle groups. Muscles are first tensed in order to create a greater contrast with the sensation of relaxation since people often are unaware that their muscles are tensed. For people with chronic pain such as that from osteoarthritis, muscle tensing can be painful so only the relaxation portion should be utilized. Autogenic training is another relaxation strategy that, like PMR, involves systematically focusing on parts of the body. However, rather than tensing and relaxing muscle groups, the individual is instructed to repeat in their mind or out loud "My [body part] is heavy and warm." By focusing on a body part and repeating this statement there is often a sensation of warmth and heaviness produced that most people find to be relaxing. Other relaxation strategies can include meditation (discussed in more detail below), listening to music, and prayer. Ultimately, what is relaxing for one person does not work for another so experimenting with various methods may be necessary.

Cognitive treatment approaches

Many patients with insomnia report that they have difficulty falling asleep because of an inability to "turn off my mind." In fact insomnia can be related to a form of performance anxiety inasmuch as the more someone thinks about sleeping the more difficult it becomes to do so. As a result, the past 15 years have seen an increased interest in the role of cognitive treatment strategies that seek to improve sleep by changing the content and process of mental activity. Cognitive strategies are routinely integrated with behavioral approaches producing a blended cognitive-behavioral treatment and some have even examined the efficacy of cognitive strategies alone [19]. A number of strategies can influence cognitive processes including the distracting nature of relaxation exercises. It has even been proposed that stimulus control and sleep restriction work in part through cognitive means because they both drastically cut down time spent in bed awake when an individual would likely be engaging in unhelpful cognitive activity [20]. Currently, there are three cognitive approaches that have been described in the literature.

Dysfunctional beliefs about sleep

In Beck's initial formulation of cognitive therapy, depressed patients were reported to engage in negative cognitive processing that reinforced and even worsened their depressed mood [3]. Cognitive therapy has clearly demonstrated that these cognitive processes can be changed, leading to improvement in mood. Similarly, patients with insomnia often process information in a way that maintains and worsens their sleep. This often takes the form of beliefs about that sleep such as "I must have 8 hours of sleep to feel rested" or "without a good night of sleep I can not function the next day." There is a certain ingredient of truth in these statements in that a poor night of sleep can impair functioning the following day and longitudinal data has shown higher mortality rates for patients at the extremes of the sleep duration spectrum [21]. However, these beliefs can be held to such a strong degree that any difficulty sleeping is interpreted as having catastrophic consequences, fueling sleep-related anxiety and cognitive arousal, and making sleep onset even more unattainable [22].

As in the treatment of depression, cognitive therapy can be used to change these dysfunctional beliefs as a means of improving sleep. Patients first need to identify those sleep-related beliefs that they hold strongly. This can be accomplished through self-monitoring of sleep-related thoughts, or through completion of the Dysfunctional Beliefs and Attitudes about Sleep scale, which was designed specifically to identify these beliefs [22]. Once the patient's dysfunctional beliefs are identified a "collaborative empiricist" stance is taken and they are taught to challenge these beliefs and examine the evidence that does or does not support them. Over time, the strength of these beliefs is reduced and there is less cognitive interference with sleep.

Behavioral experiments

One criticism of challenging dysfunctional beliefs is that purely mental approaches are insufficient to

promote cognitive change and that learning by experience is necessary. Behavioral experiments can be designed that create experiential learning situations that challenge dysfunctional beliefs about sleep and foster the development of more adaptive ways of thinking [23]. For example, if an individual has the strongly held belief that "Without 8 hours of sleep I cannot function" then they can be given the assignment of intentionally sleeping less than 8 hours. Initially, they would be instructed to monitor their sleep and to rate their daytime level of functioning for 1 week. This should ensure that there is a sampling of "good" and "bad" nights. For the next 2 nights they could be told to intentionally go to bed later while maintaining the same wake-up time in order to curtail total sleep time, while continuing to rate daytime functioning. The ratings of daytime functioning for these restricted nights would be compared with those from "good" nights. Functioning ratings would likely be lower after a restricted night but still considerably higher than zero. This can help the patient to see that, while functioning is not optimal following reduced sleep time, he or she is still able to make it through the day and may even have days that were not affected by sleep loss. The experiential nature of this learning can lead to greater cognitive change than challenging these thoughts alone. A number of these experiments can be used as a means to change dysfunctional cognitive patterns. There are a number of nuances to the design and implementation of behavioral experiments that need to be considered in order for them to be effective.

Mindfulness and acceptance

Cognitive therapy traditionally is an active form of therapy that focuses on changing dysfunctional patterns of thinking. In recent years there has been a growing recognition of the equally important role that *acceptance* can play in therapy, where patients learn to cope with their current state rather than trying to change it [24]. Acceptance of problems can promote healthier adaptation and coping, leading to a subsequent reduction in distress. In the context of insomnia, acceptance would entail focusing on the experience of insomnia rather than attempts to change sleep. Acceptance can lead to a decrease in sleep-related anxiety that was acting as a perpetuating factor. The acceptance approach is somewhat paradoxical in that change can be achieved when one stops trying to effect change.

One popular acceptance strategy is the practice of *mindfulness*. Mindfulness involves disengaging from one's own cognitive processes in such a way that they can be observed and evaluated by "paying attention in a particular way: on purpose, in the present moment, and non-judgmentally" [25]. Through mindfulness practices patients learn to observe their thoughts without explicitly trying to change them and the emotional distress produced by these thoughts is then reduced. Patients with insomnia can apply mindfulness techniques while in bed trying to sleep and reduce the emotional impact of sleep-related thoughts, thereby making it easier to fall asleep. Most of the research demonstrating the benefits of mindfulness meditation for sleep quality has been conducted in cancer patients [26, 27]. Other research has shown changes in slow wave sleep as a function of meditation [28]. However, a larger randomized trial is warranted before firm conclusions can be drawn about the efficacy of these strategies.

Models of implementation

One of the strengths of CBT-I is its flexibility. Treatment usually is conducted on an individual basis in the context of a 30- to 60-minute appointment over 8–10 sessions (see Figure 36.2). One limitation has been the paucity of healthcare providers who are versed in providing CBT-I. Given the psychoeducational nature of portions of CBT-I, some providers are delivering treatment in a group setting in which one provider works with 6–10 patients at a time in order to address this concern. There is a loss of focus on each individual with group therapy but there is an added interpersonal element in the interactions among the patients. In some cases, for the first time since developing insomnia, patients can interact with people who truly understand what they are going through. Interpersonal treatment components can be very powerful, potentially outweighing any loss in treatment efficacy due to the reduction in individualized attention. Empirical evidence indicates that group therapy can be as effective as individual therapy [29]. Several studies have also explored the possibility of self-help versions of CBT-I delivered in a reading format [30] or over the Internet [31]. Data have been mixed so far but this is one area of potential growth in the future. While CBT has been associated with sustained benefit during long-term follow-up of up to 2 years [32], others have suggested a potential benefit of a "refresher" session at 6–12 months [33].

CBT-I is also flexible in the types of patients with which it is used. Much of the research in CBT-I has

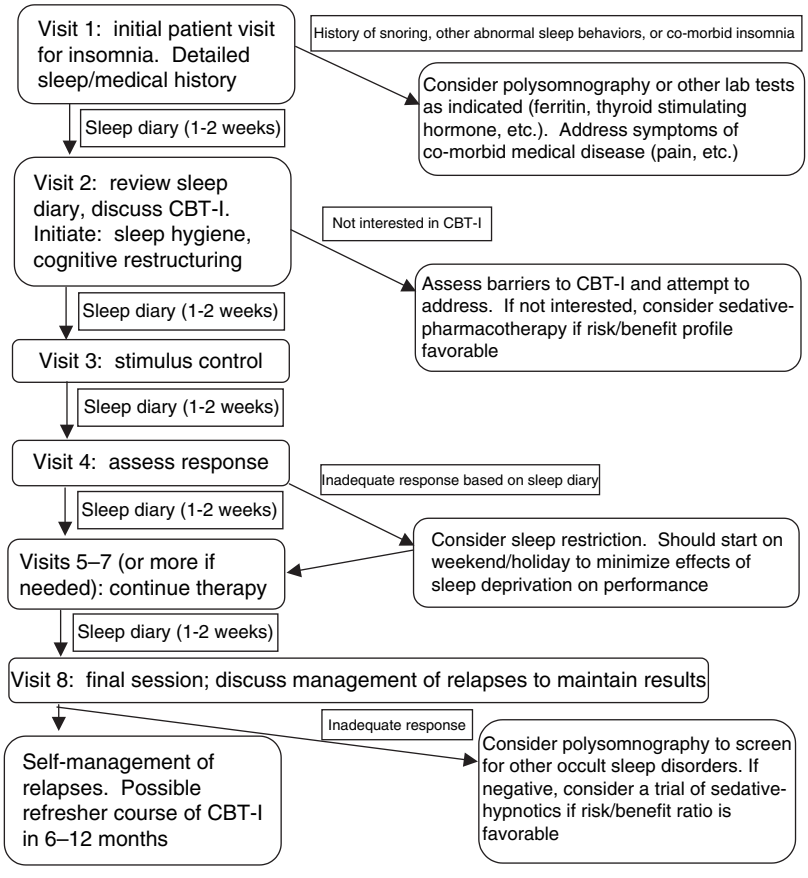

Figure 36.2. Implementation of cognitive-behavioral therapy for insomnia.

focused on cases of primary insomnia in which the sleep disturbance is an independent condition. It was thought that cases of insomnia that occurred secondary to depression, anxiety, a medical condition, or another condition were best managed by treating the supposed primary condition. However, insomnia often persists despite successful resolution of the primary condition. Over time the sleep disturbance takes on a life of its own and exists at least partially independent of the primary condition. The term "co-morbid" insomnia is now used rather than secondary insomnia to reflect the nature of the disturbance [2]. Research literature demonstrating the efficacy of CBT-I for the treatment of co-morbid insomnia is rapidly growing. There is also evidence that sleep gains made with CBT-I can lead to improvement in the primary condition such as improved ratings of mood and pain [34]. Another area of interest is the role of CBT-I in other geriatric patient care settings, such as institutionalized patients or at-home patients with cognitive impairment. Several studies have examined various CBT-I components, such as sleep hygiene or reducing daytime sleep [35]. These studies have noted beneficial effects in these patient populations, with improvements persisting up to 6 months in some cases [36]. Thus, CBT-I can be applied across the board in older adults regardless of existing co-morbidities, although the potential impact of treatment-induced sleepiness may be more significant in certain circumstances.

An important additional consideration in regards to the use of CBT-I is that patients may already be taking sedative-hypnotics or other treatments for their insomnia. While it is possible that the concurrent use of pharmacological treatments for insomnia may undermine compliance with CBT-I, pharmacological therapy may also enhance the beneficial effect of CBT-I [37]. CBT-I has also been used to taper patients off sedative-hypnotics [38].

Safety considerations

CBT-I is generally considered to be a safe therapeutic option with few known side effects. One important side-effect consideration is that of increased daytime sleepiness during the initial treatment period with CBT.

This most commonly occurs with sleep restriction therapy. Reducing daytime napping as a sleep hygiene intervention will also likely lead to an increase in daytime sleepiness until night-time sleep improves. Patients need to be aware of the potential risks of this increased sleepiness and should take the appropriate precautions before driving or engaging in other activities in which sleepiness could be dangerous. One study, for example, has explored the potential use of modafanil to ameliorate the effects of daytime sleepiness during concurrent CBT-I in younger patients [39]. Obviously patient safety needs to be of utmost priority in delivering CBT-I.

Evidence for the efficacy of CBT-I

A number of studies have now documented the efficacy of CBT-I with randomized controlled trials. Three meta-analyses have summarized these trials [40, 41] including a Cochrane review [33] and a fourth has compared CBT-I to the effects of pharmacotherapy [42]. The meta-analyses have found that CBT-I is associated with moderate to large effect sizes with larger improvements found in sleep latency (43% reduction) and nocturnal wakefulness (56% reduction) than in total time spent asleep (6% increase) [42]. The Cochrane review noted milder improvements in part due to more rigorous study inclusion criteria, but concluded that the favorable side-effect profile relative to sedative-hypnotic agents warranted consideration of CBT-I in the treatment regimen for insomnia [33]. It has also been suggested that the improvement from CBT-I may decrease with advancing age [33, 43]. When compared to pharmacotherapy, changes produced by pharmacotherapy were 30%, 46%, and 12%, respectively, suggesting that treatment outcomes produced with CBT-I are comparable or better than pharmacotherapy for most variables [42].

A review of practice parameters of various cognitive behavioral approaches for insomnia in adults (not limited to older adults), including level of evidence, was prepared by Morgenthaler *et al.* in 2006 and is summarized in Table 36.1 [44]. CBT-I was found to be effective for primary and secondary insomnia (practice parameters 3.1 and 3.2). Insufficient evidence was available to recommend one single therapy over another, or to recommend single therapy versus a combination of psychological and behavioral interventions (practice parameter 3.13).

In summary, CBT-I is a treatment that consists of a number of behavioral and cognitive strategies. The wide range of strategies available allows for tailoring of treatment to the unique needs of each individual and can be adapted for use with older adults. It is an efficacious treatment for insomnia in older adults as demonstrated across several randomized controlled trials and subsequent meta-analyses. Furthermore, it may have a more favorable risk/benefit profile than

Table 36.1. Practice parameter recommendations for the use of cognitive behavioral therapies for the treatment of insomnia in adults

Therapy	Status	Level	Practice parameter number
Stimulus control	Recommended	Standard	3.3
Relaxation training	Recommended	Standard	3.4
Sleep restriction	Recommended	Guideline	3.5
Cognitive behavior therapy	Recommended	Standard	3.6
Multicomponent (without cognitive)	Recommended	Guideline	3.7
Paradoxical intention	Recommended	Guideline	3.8
Biofeedback	Recommended	Guideline	3.9
Sleep hygiene as monotherapy	Insufficient evidence		3.10
Imagery training as monotherapy	Insufficient evidence		3.11
Cognitive therapy as monotherapy	Insufficient evidence		3.12
Psychological therapy in older adults	Recommended	Standard	3.14
Psychological therapy in chronic hypnotic users	Recommended	Standard	3.15

Adapted from [44].

pharmacotherapy in this population, which is particularly vulnerable to the effects of polypharmacy.

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Part 4
Chapter
37

Treatment of sleep disorders in the elderly

Self-help treatments for older adults with primary and co-morbid insomnia

Bruce D. Rybarczyk and Laurin J. Mack

Introduction

Insomnia is experienced by individuals of all ages but is particularly salient among adults over the age of 55 [1] with over 20% of older adults experiencing symptoms of insomnia [2, 3, 4]. Though commonly considered a primary diagnosis, insomnia often co-occurs with alcohol and drug dependence, medical and psychiatric illness, pharmacological drug use, circadian rhythm changes, and other sleep disorders especially in older adults [5]. The difficulty in determining whether these various co-existing conditions pre-date and/or exacerbate the insomnia has been widely documented [6]. Accordingly, a 2005 State-of-the-Science Conference [7] recommended that *secondary insomnia* be removed from the clinical taxonomy and be replaced with the more descriptive diagnostic term, *co-morbid insomnia*.

Mental and physical health impairments are common consequences of insomnia among older adults. Chronic insomnia leads to problems with depression and anxiety, and fatigue and is associated with declines in quality of life and health functioning [2, 8, 9, 10]. Another negative consequence of insomnia is the tremendous financial burden it places on society. Stoller [11] estimates that the total direct and indirect cost of insomnia is US$92.5 to US$107.5 billion annually, resulting from higher healthcare utilization and decreased workplace productivity. Unfortunately, relatively little attention has been paid to the public health burden of insomnia [7].

A body of research has shown that Cognitive Behavioral Therapy for Insomnia (CBT-I) is an effective treatment for middle-aged and older adults suffering from insomnia [12]. In fact, there is convincing evidence that CBT-I is an effective treatment alternative to pharmacotherapy [13, 14], which has a greater number of potential side effects (i.e. disruption of sleep architecture, reduced efficacy over time, and dependence) [15]. In addition, a review in 2005 by Smith *et al.* [16] suggested that CBT-I is equally effective for the treatment of co-morbid insomnia among individuals with a wide range of co-morbid psychiatric and medical conditions.

Only a small portion of individuals with chronic insomnia receive any treatment for their sleep difficulties despite evidence of the negative consequences of this condition and the proven efficacy of CBT-I. Behavioral interventions continue to be underused by health practitioners and largely unknown to the general public. This may be due to the fact that it is difficult to find a trained sleep professional to effectively administer the therapy [17]. Also, when individuals do seek help from their primary care physician, hypnotic drugs are usually prescribed because physicians are not aware of viable behavioral alternatives [18]. Hypnotic drugs are perceived as a cheaper and easier treatment method than psychotherapy [17]. Accessibility to behavioral interventions for insomnia is another barrier and potentially an even greater problem for older adults who may be unable to visit a clinic for the required weekly behavioral treatment sessions because of mobility and financial restrictions [19, 20, 21].

There is a critical need to make behavioral interventions for chronic insomnia more easily accessible and affordable to the general public. Self-help CBT-I treatments could play an important role in filling the treatment gap in the older adult population in particular. In this chapter, self-administered treatment or self-help is defined as any therapeutic intervention that was designed to be implemented by the client and presented in a written, audiotaped, videotaped, or computerized format (or combination thereof). Self-help programs in the form of bibliotherapy [19, 21, 22] educational audiotapes [23], videotapes [20, 24], and Internet-based programs [25] have been shown to be effective treatment modalities. A handful of studies evaluating the efficacy of self-help programs for primary and co-morbid insomnia will be reviewed in subsequent sections.

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Self-help behavior change interventions for mental and physical health problems

In an early review of the empirically supported self-help literature, Glascow and Rosen [26] reported that self-help programs have proven to be effective at least in the short term for fear reduction, exercise, weight loss, and study skills behavior. Since then, there has been a considerable body of work testing the efficacy of self-help treatments [27]. There are a range of mental and physical health issues whose response to self-administered treatment have been evaluated by research studies, such as anxiety [28, 29], depression [30, 31], bulimia [32], alcohol abuse [33, 34], smoking cessation [35, 36], chronic pain [37, 38], tinnitus [39], weight loss [40], and stress and coping [41]. Although there have been numerous positive findings, the overall evidence for the effectiveness of self-administered therapies is mixed. Generally, studies suggest that self-help treatments are effective for depression, mild alcohol abuse, and anxiety disorders but have been less successful for habit-forming behaviors such as smoking cessation and moderate to severe alcohol abuse [42, 43].

If shown to be effective, there is widespread agreement that not only can self-administered therapy be significantly more convenient and cost effective than therapist-administered treatment but also they can be accessed by a greater number of treatment seekers [26]. Additionally, self-help treatments are attractive options for people who have negative attitudes about treatment or who are apprehensive about talking to others about their problems and habits [42]. A down side to the self-help movement is there is a wide and confusing range of self-help material available and many of the methods have not been scientifically evaluated [42].

Self-help studies use differing degrees of therapist contact in their research designs, which may have a significant impact on the generalizability of their findings. Glasgow and Rosen [26] define three levels of therapist/client contact. *Self-administered* is used to describe therapy in which the clients solely administer therapy with no therapist contact other than for the purposes of assessment and data collection. *Minimal-contact* connotes primarily self-administered treatment, which could include a preliminary introduction to the self-help materials and/or periodic check-ins by the therapist, which may include weekly phone calls, emails, or occasional meetings. *Therapist-administered* treatments entail regular contact with the therapist such as meetings to clarify information presented in the self-help material. Higher levels of therapist contact have generally been found to increase self-help treatment efficacy [42].

Self-help interventions also vary in terms of the different media that are employed, including books, audiotapes, videotapes, computer-based information, or websites. According to a review by Mains and Scogin [42], self-administered therapies that utilize a combination of approaches such as telephone calls, written materials, computer programs, audiotapes, or videotapes tend to be more effective than single modality self-administered treatments. Previous research on learning suggests that individuals retain more if the information is introduced in a multi-media format. Another aspect of self-help treatment that can inform the likelihood of successful treatment is the individual characteristics of the treatment seeker. Mains and Scogin [42] also indicate that self-help treatment is not recommended for individuals with personality disorders, severe symptomology such as suicidality, emotional avoidance, or extreme interpersonal problems. Conversely, individuals who are highly motivated, resourceful, and who have an optimistic outlook towards self-help seem to have more treatment success.

Self-help and primary insomnia

There are a growing number of studies that have documented the efficacy of self-help for insomnia using a variety of different treatment delivery methods including bibliotherapy, audiotapes, videotapes, and the Internet. Simple methods of delivery (i.e. printed material) have almost certainly been driven by cost considerations, while other investigators have presumably used more sophisticated media (e.g. video, audio, and Internet) in an attempt to enhance the learning experience and make it more attractive. The Internet has the added bonus of making the material interactive (e.g. by including quizzes and sleep diaries). Two early studies were conducted prior to the emergence of multi-component CBT-I and, therefore, employed relaxation training and stimulus control only [19, 23]. Subsequent self-help studies have provided the full CBT-I package. Together there have been eight published studies on self-help treatment for insomnia. These studies and their characteristics are presented in Table 37.1.

Table 37.1. Results and characteristics of published studies of self-help treatment for insomnia

Authors and year	Population	Self-help treatment modality	Study design	Sleep measure
Alperson & Biglan 1979 [19]	Adults with PI N = 29	Manuals	– Benson's Relaxation and Instructions on Stimulus Control Procedures (BRAST) – William's Relaxation and In-bed Activities (WRAST) – Self-Monitory Only (SEMO)	Self-report
Morawetz 1989 [23]	Adults 18–60 with PI N = 159	Audiotaped and manual	– Self-help – Therapist-led – Wait-list control	Self-report
Riedel *et al*. 1995 [20]	Adults 60 + with PI N = 25	Video	– Self-help (insomniacs) – Self-help (non-insomniacs) – Self-help + therapist guidance (insomniacs) – Self-help + therapist guidance (non-insomniacs) – Wait-list control (insomniacs)	Self-report SSS
Mimeault & Morin 1999 [22]	Adults with PI N = 54	Booklets	– Self-help – Self-help + therapist guidance – Wait-list control	Self-report PSQI SII BAAS ITEQ
Ström *et al*. 2004 [25]	Adults with PI N = 109	Internet	– Self-help with therapist contact – Wait-list control	Self-report DBASS
Rybarczyk *et al*. 2002 [45]	Adults 55+ with PI N = 38	Audiotapes	– Home-based relaxation – Classroom CBT – Wait-list control	Self-report ACT PSQI DBASS
Morin *et al*. 2005 [21]	Adults with CI N = 192	Booklets	– Self-help – No treatment control	Self-report ISI PSQI
Rybarczyk *et al*. 2005 [46]	Adults 55+ with CI N = 36	Video	– Self-help – Classroom CBT – Wait-list control	Self-report PSQI DBASS

Sleep measures: actigraphy (ACT), Pittsburg Sleep Quality Inventory (PSQI), Sleep Impairment Index (SII), Dysfunctional Beliefs and Attitudes about Sleep Scale (DBASS), Stanford Sleepiness Scale (SSS), Insomnia Treatment Evaluation Questionnaire (ITEQ), Insomnia Severity Index (ISI), The Beliefs and Attitude About Sleep Scale (BAAS), Primary Insomnia (PI), Co-morbid Insomnia (CI).

The pioneer study on self-help methods in the treatment of insomnia was conducted by Alperson and Biglan [19] and compared the effects of two self-administered manuals to a wait-list control group. The first manual combined relaxation and stimulus control techniques such as leaving the bedroom to break the association between the bed and existing patterns of non-sleep behaviors. The second manual prescribed in-bed exercises and activities, as an alternative to stimulus control. Volunteers were recruited via newspaper advertisement offering free experimental help for improving sleep latency. All participants in the experimental group met with a study therapist three times over a 12-week period for instruction and clarification of how to follow the self-help manuals. The results of the study indicated that both manualized self-administered treatments for insomnia were effective for improving sleep latency among younger adults as compared to self-monitor only control group. A comparison of older and younger adult participants in the relaxation and stimulus control condition showed that such treatment was not as effective for the 55+ age group participants.

Almost a decade later, Morawetz [23] conducted a controlled study of self-help treatment for insomnia that employed manual and audiotape instruction [44] in stimulus control and relaxation techniques. The study design included a self-help treatment group, an equivalent therapist-led group treatment, and a no-treatment control group. The sample included a population of adults between the ages of 18 and 60 with primary insomnia and had only an 11% dropout rate. Results showed that the self-help treatment and therapist-led treatment were equally effective in improving sleep relative to controls, but only the therapist-led treatment was effective for individuals currently using sleep medication.

A study by Riedel *et al.* [20] was the first and only study to date that has looked at the efficacy of self-help video treatment in a sample of older adults with primary insomnia. The design included a wait-list control group and two treatment groups, self-help video only and a self-help video plus therapist guidance for sleep schedule changes. The treatment groups had both insomniacs and a control group of insomniacs to test the effects of sleep restriction on a "normal" older adult population. The video provided sleep education and instruction on sleep compression (i.e. a form of sleep restriction). The results revealed that the self-help video helped older adults improve on multiple self-report sleep variables compared to controls and there was some enhancement of outcome with the addition of therapist guidance. This enhancement could have been due to the greater compliance with treatment instructions in the therapist-led group, which indicates that future studies of self-help for insomnia might well include treatment compliance strategies in their treatment material. These results provided the first evidence that self-administered treatments for insomnia could be effective for older adults as well as younger adults with insomnia. Other interesting results of the study were that older adults suffering from insomnia did not show significantly less sleep knowledge as compared to older adults not suffering from insomnia.

In a later study by Mimeault and Morin [22], the effects of self-help CBT-I bibliotherapy on adults with primary insomnia were evaluated. Participants were randomized to a self-help treatment, self-help with phone consultations, or a non-treatment wait-list control group. CBT-I booklets were mailed to participants in the treatment groups, each covering a component of the treatment for 6 weeks. Participants in the self-help with phone consultations condition received 15-minute bi-weekly therapist phone consultations during which therapists answered questions about treatment procedures and encouraged study compliance. Participants in both treatment groups exhibited significant improvements in total wake time and sleep efficiency at post-treatment as compared to wait-list controls. Although the therapist guidance treatment did show minimally enhanced improvements at post-treatment, results at a 3-month follow-up assessment indicated that the self-help treatment had comparable effects to self-help with adjuvant therapist phone calls. These results provide evidence that improvement in sleep resulting from self-help can be maintained over time.

A recent study by Ström *et al.* [25] used an innovative Internet-based CBT-I program with limited email support from therapists to target adults with primary insomnia. Participants were recruited via newspaper and web articles. Of the 109 participants who were included in the study, 24 dropped out before completion of the protocol. Participants were randomized to either the Internet-based sleep management program or a wait-list control group. The Internet treatment program provided for interactive CBT-1 information and allowed for sleep data to be entered electronically by participants and transmitted over the web to sleep

therapists. The study found significant improvements on a range of sleep measures including total sleep time, total wake time in bed, and sleep efficiency in the Internet self-help treatment group relative to a wait-list control condition.

A recent study by Morin and colleagues [21] selected adults with insomnia from a larger randomly selected community epidemiological study. The 192 participants were randomly assigned to a self-help treatment or a no-treatment control group (20 participants dropped out before the conclusion of the protocol). The self-help treatment paralleled the bibliotherapy employed in Mimeault and Morin's 1999 study [22]. In this case, a toll-free number was provided for the participants to be called if they had questions about the treatment procedures. The research found significant self-report sleep benefits at post-treatment and 6-month follow-up in the self-help condition as compared to the control group, though results were attenuated compared to prior in-person CBT-I studies. Nonetheless, these findings suggested that self-help is a viable form of therapy for alleviating insomnia in a non-self-referred, community-based sample of adults with insomnia and produces results that are maintainable over time.

Self-help for co-morbid insomnia in older adults

Three studies to date have evaluated self-administered treatment for insomnia in older adults with co-morbid medical illness. The first was a study by Rybarczyk *et al.* [45], which included adults over the age of 55 with insomnia that was co-morbid with a range of chronic medical conditions. Participants were recruited using a patient database from a health maintenance organization (HMO) office. A list of eligible older adults was generated and telephone calls were placed to determine if patients were suitable for the study. Participants were randomized to one of three conditions: classroom CBT-I, home-based audio relaxation treatment (HART), or delayed treatment control. The HART treatment consisted of seven commercially available relaxation audiotapes to be employed over 6 weeks. A booklet with sleep education information was also provided. The study co-ordinator made weekly phone calls to the HART participants to encourage study compliance and answer any questions about the treatment material that could have come up.

Results from the study revealed that compared to the control group, the CBT-I group had significant changes in five of seven self-report measures of sleep at the 4-month follow-up. The HART group obtained significant outcomes on three of seven measures. Clinically significant changes at follow-up were obtained for 54% of patients in CBT, 35% in HART, and 6% in the control group when treatment dropouts were included. These results indicate that the self-help HART program, though not as effective as the classroom CBT-1 treatment, could provide a less expensive alternative to therapist-led CBT-I.

Rybarczyk *et al.* [46] reported on an additional randomized, treatment-delayed self-help group that was compared to classroom and wait-list control groups in the Rybarczyk *et al.* 2002 study [45]. This self-help intervention consisted of a eight 1-hour videotapes that were taped from the classroom CBT-I along with a set of support reading materials. The use of a videotape copy of the classroom intervention was effectively employed in a previous study aimed at enhancing the coping and wellness of a group of older adults with chronic illness [47]. Results of the study indicated that compared to wait-list controls, the video CBT-I group demonstrated significant changes in five of eight self-report measures of sleep at post-treatment. The self-help CBT-I was not significantly different from classroom CBT-I on self-report measures of sleep, although the attrition rate was higher (27% vs. 19%) and the number of participants who achieved clinically significant change was significantly lower. This was the first study to specifically look at the efficacy of CBT-I self-help treatment for older adults with co-morbid insomnia and added to the existing evidence [45, 48] that CBT-I is as effective for individuals with co-morbid insomnia as for those with primary insomnia

The previous two studies led to a larger study by Rybarczyk and colleagues (unpublished data), which tested two methods of self-help CBT-I among 106 older adults (mean age = 68) with no significant medical condition (N = 40), osteoarthritis (N = 33), or coronary artery disease (N = 33). All participants were randomly assigned to a book version or an enhanced multimedia version of CBT-I, which was predicated on the previously cited work indicating that self-help treatments may be more efficacious if they are delivered via multi-media as compared to single media [42]. Due to the previous studies supporting the efficacy of self-help treatment for insomnia, rather than

including a wait-list control group, the study compared two treatments and employed a primary insomnia treatment group. Both versions of CBT-I demonstrated efficacy in improving all measures of sleep at post-treatment, using intent-to-treat analyses. The results also yielded no significant differences in treatment response between primary (i.e. no co-morbid medical condition) and co-morbid insomnia participants. There were no significant differences between the two types of self-help CBT-I on sleep diary measures, but multimedia participants showed more improvement on three global sleep measures compared to book participants. The sleep improvements were maintained among the 66 participants who participated in a 1-year follow-up assessment. Both methods of CBT-I improved daytime mood and health functioning at post-treatment, but only anxiety reductions and vitality increases were sustained at 1-year follow-up. These results, combined with previous studies, strongly suggest that CBT-I delivered in a self-help format has the potential to serve as a first-line, cost-effective treatment for both primary and co-morbid insomnia in older adults.

Summary

In summary, accumulating evidence has shown that self-administered therapy delivered in various forms, including bibliotherapy, audiotapes, video- and Internet-based protocols, is on a par or only slightly less effective than therapist-led CBT-I. Several studies confirm that these interventions are efficacious in both older and younger adult samples, and with primary and co-morbid insomnia populations. These finding are consistent with previous work on self-help interventions for a range of behavioral issues. This approach to the treatment of insomnia holds much promise for serving as a cost-effective and more accessible alternative to in-person CBT for the large segment of the population that currently receives no treatment for chronic insomnia. Many of these individuals have failed a course of pharmacological treatment or prefer not to become dependent on another medication, as is often the case with older adults who are already taking numerous medications.

Nonetheless, it should be emphasized that research in this important area is still in its nascent stages and much work is needed to confirm and refine previous findings. For example, a randomized controlled study that directly compares self-administered treatment with therapist-administered treatment for primary and co-morbid insomnia in older adults would be an appropriate next step. In addition, studies need to be done to determine what characteristics predict successful self-help treatment, so that decisions can be made about what types of patients to refer to self-help. As self-help treatments begin to be tested with clinically referred populations there is likely to be a higher rate of attrition and lower rates of compliance relative to the predominantly volunteer-driven studies done thus far. Furthermore, no studies as of yet have reported outcomes that are verified by polysomnography and only one study reported non-significant actigraphy data [45].

Another area to be further elucidated is the role of therapist guidance in self-help for insomnia in older adults. What degree of therapist contact, if any, would provide the most effective treatment while not compromising the convenience and cost benefits of self-help therapy? In the existing studies summarized above, only three studies [20, 22, 25] compared the effects of different degrees of therapist/client contact. More research in this area clearly needs to be completed to establish the most beneficial level of therapist/client contact for different types of insomnia and different populations. This will be particularly important if and when self-help treatments are prescribed to individuals who are referred by healthcare providers and need more direction than the predominately self-referred individuals included in the research thus far.

The prolific number of self-help books on the market illustrates the consumer demand for self-administered treatments. The authors conducted an informal search on Amazon.com to find how many self-help books were available. There were over 22 self-help books, DVDs, and CDs that were available for insomnia treatment. Of these, only a small percentage appears to adhere to empirically validated CBT-I protocols. Until the effectiveness of these other hybrid approaches are tested in randomized studies, self-administered treatments should be approached and recommended with caution and good clinical judgment [42].

Traditionally, self-help treatments have employed a variety of modalities such as books or manuals, audiotapes, and videotapes. More recently, computer-based programs have become popular [42]. Computerized treatment program packages allow for more patient interaction with the therapeutic material and provide for the information to be delivered in different formats, which could serve to enhance learning and maintain the client's interest and focus throughout

the duration of the sessions [49]. As the field of insomnia research progresses and the general public becomes more aware of effective behavioral treatment, there will be more self-help Internet interventions that follow in the footsteps of Ström *et al*.'s 2004 study [25]. The use of the Internet will further cut down on treatment costs and enhance accessibility to a wide range of people. Older adults, however, may not have access to computers or the Internet and may have greater trouble participating in the therapy because they are not as accustomed to computers or the Internet.

A promising application of self-help therapies for insomnia, as well as other physical and medical problems that respond to behavioral treatment, is encompassed in a stepped-care model [50]. In order to begin to address the high rates of insomnia, Edinger [51] has suggested that the first line of treatment should be to increase public knowledge of insomnia and behavioral treatment using mass media. In such a model, the first and most basic line of treatment should be the most accessible and cost effective available, namely mass-media public health education. If the initial level is ineffective for the individual's ailment, the next steps becomes incrementally more intense, beginning with the self-help protocols described in this chapter. Subsequent levels of insomnia treatment might be to obtain therapist guidance from a trained sleep nurse in one's primary care office, participate in a group treatment led by a psychologist, and, if necessary, the final level would be individual treatment by a psychologist. This model has already been addressed in a variety of clinical research areas including eating disorders [52], alcohol problems [53], generalized anxiety disorder [54], and panic disorder [55].

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Part 4
Chapter
38

Treatment of sleep disorders in the elderly

Complementary and alternative medicine for sleep disturbances in the elderly

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Complementary and alternative medicine

Complementary and alternative medicines (CAM) encompass a very diverse array of treatment modalities and diagnostic techniques. They have in common that they are not presently considered part of conventional/mainstream medicine and emphasize a holistic approach towards health care. A number of terms and definitions exist (Table 38.1) that define CAM mostly by what it is not, for example, not provided in routine health care, not taught to medical students, not scientifically proven.

The term CAM has established itself as an umbrella term for "alternative medicine" (a term popular in the 1970s and 1980s highlighting that CAM treatment approaches are used *instead* of conventional treatments) and "complementary medicine" (describing treatments used *in addition* to conventional medicine). The focus of the term has therefore shifted from mainly meaning "outside the mainstream medical system" to describing a group of therapeutic approaches that are (sometimes wrongly) associated with certain similar characteristics such as "holistic," "natural," and "harmless." Nowadays "integrative medicine" or "integrated medicine" have become buzz words claiming to comprise "the best of both systems" by combining conventional with CAM treatments for which high-quality evidence of effectiveness and safety exists – which is basically the same as evidence-based medicine.

Herbal and non-herbal dietary supplements, acupuncture, manipulative therapies, homeopathy, and mind–body interventions are among the most popular CAM modalities used by the general population but many more exist. The US National Center for

Table 38.1. Definitions of CAM

Definition	Source
'CAM is a group of diverse medical and health care systems, practices, and products that are not presently considered to be part of conventional medicine.'	National Center for Complementary and Alternative Medicine, USA http://nccam.nih.gov/health/whatiscam/#1
'CAM refers to a broad set of health care practices that are not part of a country's own tradition and not integrated into the dominant health care system. Other terms sometimes used to describe these health care practices include "natural medicine", "non-conventional medicine" and "holistic medicine".'	World Health Organization. Guidelines on developing consumer information on proper use of traditional, complementary and alternative medicine. Geneva: World Health Organization;2004:xiii
'Complementary medicine refers to a group of therapeutic and diagnostic disciplines that exist largely outside the institutions where conventional health care is taught and provided.'	Zollman C, Vickers A. What is complementary medicine? BMJ 1999;319:693–696
'CAM is a broad domain of healing resources that encompasses all health systems, modalities, and practices and their accompanying theories and beliefs, other than those intrinsic to the politically dominant health systems of a particular society or culture in a given historical period.'	Cochrane Collaboration, http://www.compmed.umm.edu/Cochrane/
'Complementary medicine is diagnosis, treatment and/or prevention which complements mainstream medicine by contributing to a common whole, satisfying a demand not met by orthodoxy, or diversifying the conceptual framework of medicine.'	Ernst E, Resch K L, Mills S, Hill R, Mitchell A, Willoughby M, White A. Complementary medicine – a definition. Br J Gen Pract 1995;309:107–111

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Published by Cambridge University Press.

Complementary and Alternative Medicine (NCCAM) has classified CAM and categorized it into several groups, acknowledging that overlaps between groups exist [1]:

- **Alternative medical systems.** These are complete systems of theory and practice. Examples of alternative medical systems that have developed in Western cultures include homeopathic medicine and naturopathic medicine. Examples of systems that have developed in non-Western cultures include traditional Chinese medicine and Ayurveda.
- **Mind–body interventions.** These are interventions using a variety of techniques designed to enhance the mind's capacity to affect bodily function and symptoms. Examples include meditation, prayer, mental healing, and therapies that use creative outlets such as art, music, or dance.
- **Biologically based therapies.** These therapies in CAM use substances found in nature, such as herbs, foods, and vitamins. Examples include dietary supplements and herbal products.
- **Manipulative and body-based methods.** These methods in CAM are based on manipulation and/or movement of one or more parts of the body. Some examples include chiropractic or osteopathic manipulation, and massage.
- **Energy therapies.** These therapies involve the use of energy fields. Biofield therapies are intended to affect energy fields that purportedly surround and penetrate the human body. Examples include qigong, Reiki, and therapeutic touch. Bioelectromagnetic-based therapies involve the unconventional use of electromagnetic fields, such as pulsed fields or magnetic fields.

These treatment modalities enjoy an ever increasing popularity with patients. Patients are attracted to CAM because its philosophy matches their beliefs about health and illness. They are drawn by the spiritual dimension, fundamental components such as vitalism, and the enhancement or balancing of "life forces," "qi," "psychic energy," which are central to many CAM therapies. Many forms of CAM have long traditions, sophisticated philosophies, or complex systems and concepts. This is perceived as contributing to their credibility and authority. CAM's emphasis on holism and the use of "natural" treatments are perceived as attractive. Unfortunately, "natural" is often wrongly equated with "safe," which can be dangerous in general but in particular to older adults who are likely to be taking medication for a range of health complaints.

CAM users feel that they are taking an active role and have more control over their health and treatment. Patients' choice is an important element: CAM is perceived as one of many treatment options and patients exercise their freedom of choice. The finding that CAM use is associated with higher levels of income seems to support the concept.

CAM users also report a better relationship with their CAM practitioner than with their mainstream physician. They feel on equal terms with their CAM practitioner who has more time for discussion and allows for emotional factors. CAM tends to be person-centered and human experience is a central element of it.

Rejection of or dissatisfaction with conventional medicine, e.g. with ineffective treatments, adverse effects of treatments, poor communication, and/or insufficient time with doctor, are pushing patients towards CAM. Desperation is also a determining factor for CAM use as particularly chronically and terminally ill patients do not wish to leave any stone unturned.

Use of CAM in the elderly

Studies report a high prevalence of CAM use in the elderly. In a recent telephone survey of 1559 people over the age of 50, 63% reported using CAM [2]. Persons aged 50–54 years (69%) and 55–64 years (70%) were more likely to have used a CAM therapy or practice than those age 65 and older (54%).

The 2002 US National Health Interview Survey including the Alternative Health Supplement suggests that CAM use is high in elderly patients with certain conditions; it reports that among adults aged 65 or over, almost 70% of those with hypertension and over 80% of those with anxiety or depression used CAM for any indication [3].

Older adults often use CAM to treat chronic pain conditions such as arthritis or back pain, as well as a range of remedies to treat other age-related ailments such as, for example, the herbal remedies *Ginkgo biloba* and *Panax ginseng* to improve cognitive function [4]. Approaches frequently used by the elderly are chiropractic, massage or other body work therapies (45%), herbal and other dietary supplements (42%), followed by mind–body practices including

hypnotherapy and meditation (15%), as well as acupuncture, homeopathy, naturopathy (14%), and energy therapies (10%) [2].

CAM use in older adults presents several unique and important issues. Older adults often present with various health complaints and the majority of patients with insomnia also have co-morbidities [5]. Elderly patients therefore use a variety of CAM concurrently with other medical treatments to improve health outcomes. They often self-medicate for other complaints with allegedly "natural" remedies without considering or discussing safety aspects with their physician. Three-quarters (75%) of the respondents to the above-mentioned telephone survey who in their lifetime had ever used herbal products or dietary supplements reported that they currently take one or more prescription medicines [2]. An alarmingly high proportion of these (77%), however, do not discuss their CAM use with their healthcare provider. This is a serious issue as interactions with prescription or other self-administered drugs are pertinent. Patients should therefore be specifically asked about their CAM use and informed about any safety issues. In particular, the use of herbal and other dietary supplements should be assessed as there is potential for interactions with drugs or other CAM modalities and their safety has in many cases not been established beyond reasonable doubt.

Little of the clinical evidence on CAM has been derived from studying elderly patients. Trial data are usually extrapolated from one age group to another and it is assumed that if it works in the middle-aged or younger individuals, it is also effective in the elderly. Physiological changes relating to digestion, metabolism, and excretion of ingested products that may impact the metabolism of drugs, herbs, and other dietary supplements need to be considered in the elderly. Furthermore, osteoporosis is particularly common in the elderly, especially in women, which has important implications for a range of physical CAM approaches such as vigorous spinal manipulation or even vigorous massage. Declining cognitive abilities and generally age-related differences in health beliefs might affect the effects of mind–body therapies.

CAM and sleep in the elderly

Pearson *et al*. analyzed data from the 2002 National Health Interview Survey relating to insomnia and trouble sleeping in the general population [5]. Of those with insomnia or trouble sleeping, 4.5% reported using CAM to treat their sleep disturbances. Although this percentage seems surprisingly low, it still amounts to over 1.6 million people in the USA. The odds of insomnia or trouble sleeping increased with age, peaking in middle age (45–54 years), then decreased slightly during old age (65–84 years), followed by an increase at very old ages (≥85 years).

Individuals using CAM for their sleep disturbances mainly used biologically based therapies such as herbal and other supplements (64.8%) and mind–body therapies (39.1%), followed by alternative medical systems such as acupuncture (8.5%), and manipulative treatments (4.6%) [5]. Pearson points out that those without co-morbidities preferred mind–body therapies, while those with co-morbidities preferred biologically based therapies – another indicator that concurrent use of prescription medication and over-the-counter products in the elderly is high and needs to be monitored.

Many CAM modalities are promoted for health and relaxation and thus for facilitating sleep (Table 38.2), with melatonin and valerian being among the most popular [6, 7]. For only a few of them, however, effectiveness has been evaluated using objective sleep measures [8]. This chapter focuses on treatments that are frequently used to treat sleep disturbances and for which effectiveness and safety have been assessed in controlled clinical trials (CCTs) or randomized clinical trials (RCTs) [9, 10]. For many CAM modalities there is a paucity of effectiveness data in elderly subjects. Therefore, data obtained from studies involving younger subjects have been included where appropriate.

Evidence and safety of biologically based therapies for insomnia

Melatonin

Melatonin is a neurohormone produced by the pineal gland postulated to play a significant role in the circadian rhythm. Release is stimulated by darkness and suppressed by light. Numerous studies have shown decreased melatonin levels in the elderly. Deficiency is caused by three potential factors: medications (particular beta-blockers and non-steroidal anti-inflammatory drugs), age-related changes, and melatonin suppression from co-morbid medical conditions. The association of insomnia with serum melatonin deficiency is unclear.

Exogenous, commercially available melatonin is usually produced synthetically. Studies conducted in the 1970s and 1980s suggest sedative effects of

Table 38.2. Evidence and safety of CAM for sleep disturbances

Treatment	Description	Evidence base	Evidence of effectiveness	Safety
Melatonin	A neurohormone produced by the pineal gland postulated to play a significant role in the circadian rhythm. Exogenous melatonin is produced synthetically	Several systematic reviews: 6 RCTs (N = 95) in older adults; 17 RCTs (N = 284) in general population; 14 RCTs (N = 279) in primary sleep disorders; 6 RCTs (N = 97) of secondary sleep disorders	Evidence suggests that melatonin may be of limited clinical use for primary sleep disorder No evidence that melatonin is effective in treating secondary sleep disorders or sleep disorders accompanying sleep restriction	Relatively safe if used short term and in recommended doses. Interactions must be considered
Valerian (*Valeriana officinalis, V. edulis*)	A herbaceous perennial with a long history of medicinal use. Valepotriates and amino acids are its main constituents	Systematic review of 29 CCTs (N = 1941), three thereof in older adults	Overall no significant differences between placebo and valerian	Generally safe if used in recommended doses but interactions must be considered
Kava (*Piper methysticum*)	A plant native to the South Pacific, kavapyrones are thought to be the active ingredients	Two controlled clinical trials, none specific in the elderly	Evidence for kava in sleep disturbances is contradictory	Has been linked to a number of cases of hepatotoxity
Acupuncture	Insertion of one or more needles into the skin and underlying tissues at acupuncture points for therapeutic or preventative purposes	Systematic review of 7 RCTs (N = 590)	Acupuncture may improve sleep quality scores but inconsistent efficacy for many sleep parameters	Generally safe if applied by a trained and responsible therapist, serious adverse events are on record but rare
Relaxation techniques	Techniques for eliciting the 'relaxation response' of the autonomic nervous system	Systematic review including 6 RCTs of relaxation (N = 638), two thereof in older adults	Generally superior results of relaxation compared with controls	Generally safe
Yoga	Ancient Indian practice involving postural exercises, breathing control and meditation	Two RCTs, one in older adults (N = 69), one RCT in cancer patients	Improvement in self-reported sleep measures in elderly patients with yoga, results for cancer patients are contradictory	Generally safe if common sense is applied
Tai chi	A system of movements and postures used to enhance mental and physical health rooted in ancient Chinese philosophy	One RCT (N = 118) in older adults	Improvement in self-rated sleep parameters	Generally safe if common sense is applied
Music therapy	Receptive music therapy, i.e. listening to music rather than active music making is used for sleep disturbances	One RCT (N = 60)	Better sleep quality with music therapy	Virtually risk-free

exogenous melatonin, although the basic mechanism by which melatonin produces sleepiness in humans remains unclear. Three main hypotheses have been proposed; the mechanism may involve a phase-shift of the endogenous circadian pacemaker, a reduction in core body temperature, and/or a direct action on somnogenic structures of the brain. The effects of melatonin on sleep have been evaluated in a number of controlled trials.

Evidence of effectiveness

An earlier systematic review of six double-blind, crossover RCTs including 95 patients (mean age 65–79 years) assessed sleep quality objectively measured by wrist actigraphy (N=4) and polysomnography (N=2), as well as subjectively measured (N=2) [11]. Sleep latency decreased significantly in four studies and other measures of sleep quality (sleep efficiency, total sleep time, and wake time during sleep) improved in three studies. Subjective sleep quality did, however, not improve. No early morning sleepiness occurred. Based on a comparison of these studies the authors concluded that melatonin is most effective in elderly insomniacs who chronically use benzodiazepines and/or with documented low melatonin levels during sleep.

Newer systematic reviews are based on trials including patients from across the age groups. In a meta-analysis of 17 double-blind RCTs including 284 participants, melatonin treatment was reported to reduce sleep onset latency by 4.0 minutes, increase sleep efficiency by 2.2%, and total sleep duration by 12.8 min [12].

Buscemi *et al*. performed meta-analyses of melatonin for both primary and secondary sleep disorders [13, 14, 15]. Fourteen controlled trials of exogenous melatonin for treating primary sleep disorders were included in the first meta-analysis [14]. The primary analysis showed an average reduction in sleep onset latency of 11.7 minutes, which, although statistically significant, appears to be clinically not relevant. Results for sleep efficiency, sleep onset, total sleep time, and percentage time spent in REM sleep were not statistically significant. There was substantial heterogeneity among the studies. In a secondary analysis of a subpopulation with delayed sleep phase syndrome, the average reduction in sleep onset latency increased to 38.8 minutes, which is both clinically and statistically significant. This result is, however, based on only two studies involving less than 30 participants and thus necessitates further research to confirm the results. Sleep onset latency was decreased marginally in patients with insomnia. With regard to age, sleep onset latency was reduced more in children under the age of 17 than in adults or patients aged 65 and over. The effects of melatonin did not vary with dose or duration of treatment. The authors of the meta-analysis concluded that the evidence suggests that melatonin may be of limited clinical use for primary sleep disorder.

The meta-analysis of melatonin for secondary sleep disorders including six RCTs with 97 participants showed no evidence that melatonin had an effect on sleep onset latency [15] and that the effects of melatonin did not differ between children and adults and did not vary with dose or duration of treatment. Nine randomized clinical trials with 427 participants showed no evidence that melatonin had an effect on sleep onset latency in people who had sleep disorders accompanying sleep restriction. The authors concluded that there is no evidence that melatonin is effective in treating secondary sleep disorders or sleep disorders accompanying sleep restriction, such as jet lag and shift work disorder.

Safety of exogenous melatonin

Based on available studies and clinical use, melatonin is generally regarded as safe in recommended doses (0.01–10 mg) for short-term use. Available trials report that overall adverse effects are not significantly more common with melatonin than placebo [14, 15]. The most commonly reported adverse effects of melatonin were nausea, headache, dizziness, and drowsiness; however, these effects were not significant compared to placebo. This result did not change by dose, the presence or absence of a sleep disorder, type of sleep disorder, duration of treatment, gender, age, formulation of melatonin, or use of concurrent medication. Daytime sleepiness has also been reported in younger people.

Based on case reports, concerns have been raised about risks of blood clotting abnormalities (particularly in patients taking warfarin), increased risk of seizure, disorientation, and depression. Melatonin is contraindicated in autoimmune disease, hepatic insufficiency, cerebrovascular or neurological disorders, patients taking immunosuppressants or corticosteroids, as well as in pregnancy or women trying to become pregnant. Study results of melatonin's effects on blood pressure are contradictory; patients should therefore be closely monitored. Caution is advised in

patients with diabetes or hypoglycemia as elevated blood sugar levels (hyperglycemia) have been reported in patients with insulin-dependent diabetes, and low doses of melatonin have reduced glucose tolerance and insulin sensitivity.

Valerian (*Valeriana officinalis*)

Valeriana officinalis is one of over 200 members of the Valerianaceae family. A herbaceous perennial, it is native to most of Europe and Asia and grows in damp swampy areas. The name *Valeriana* derives from the Latin word *valere* meaning well-being. Its use as a medicinal herb dates back to Hippocrates' time. *Valeriana edulis* is widely used in South America for insomnia and anxiety. Its main constituents are valepotriates and amino acids (gamma-aminobutyric acid). The exact mechanisms of actions are unclear, but the valerenic acid constituent might increase GABA activity in the central nervous system by inhibiting an enzyme that metabolizes GABA.

Evidence of effectiveness

Earlier systematic reviews and meta-analyses concluded that the effects of valerian were promising but not conclusive [16, 17]. A 2007 systematic review, however, concluded that most of the 29 clinical studies included found no significant differences between valerian and placebo either in healthy individuals or in persons with general sleep disturbances or insomnia [18]. None of the most recent studies, which were also the most rigorous, found significant effects on sleep. A subsequently published trial is in line with these findings [19]. The review paid specific attention to the differences in source species and preparation techniques used. Ethanolic extracts of *V. officinalis*, for which high-quality research evidence is available, have not been shown to significantly affect objective or subjective sleep outcomes in comparison to placebo in subjects with or without insomnia but seem to improve subjective sleep quality ratings equivalent to benzodiazepines. Studies testing the effects of aqueous valerian extracts produced mixed results. There is limited evidence that valepotriates improve sleep but these studies are highly varied. Findings for valerian combination products with hops, lemon balm, or passion flower are also mixed and predominantly negative, and indicate that combinations are not more effective than valerian alone. Three studies included older persons with sleep disturbances. Although one study concluded that a significant proportion reported "better" sleep [20], studies were not uniformly positive.

Safety of valerian

The above review also assessed safety aspects and included an additional eight open-label studies in the safety assessment [18]. It did not find any serious adverse effects in the reported studies. Most common were dizziness, headache and drowsiness, or, mainly with high-valepotriate preparations, gastrointestinal complaints. Performance seems to be little or not at all impaired with valerian especially when compared to benzodiazepines.

There are case reports of valerian and transient impaired liver function. Concerns have been raised over the safety of ingesting valepotriates and that the gastrointestinal tract is particularly at risk from adverse events. These products should be used with caution until further comprehensive safety data are available. Little evidence exists on potential herb–drug interactions of valerian. Concomitant intake of other sedative substances should be avoided due to the risk of over-sedation. Valerian is contraindicated in pregnancy and lactation due to the lack of available safety data.

Kava (*Piper methysticum*)

Native to the islands of the South Pacific, kava, the beverage prepared from the rhizome of *Piper methysticum*, has long been used for medicinal and recreational purposes. The name kava is derived from the Polynesian word *awa* or *kava* meaning bitter and refers to the characteristic taste of the beverage. At the beginning of the twentieth century scientists isolated a number of compounds which were called kavapyrones and are thought to be the active principle of kava. Studies suggest that kavapyrones act on the central nervous system. They are thought to mediate effects on GABA receptors, particularly in the hippocampus and amygdala complex. Central nervous effects of kavain and kava extract have also been demonstrated in studies on human volunteers using EEG measurements.

Evidence of effectiveness

Only limited and contradictory evidence exists for kava in the treatment of sleep disturbances. "Quality of sleep" and "recuperative effect after sleep" after 4 weeks of double-blind treatment compared

to baseline demonstrated statistically significant group differences in favor of kava extract WS 1490 in sleep disturbances associated with anxiety disorders [21]. An Internet-based RCT comparing kava with valerian and placebo (included in the above valerian review [18]) found that neither kava nor valerian relieved anxiety or insomnia more than placebo [22]. Data from studies specifically in the elderly are not available.

Safety of kava

Safety concerns have been raised about kava as it has been linked to a number of cases of hepatotoxicity. It has been banned in several countries but is still available in the USA. Adverse effects include stomach complaints, tremor, headache, drowsiness, restlessness, dyskinesia, mydriasis, allergic skin reactions, kava dermopathy, dermatomyositis, and liver damage. Kava is contraindicated in pregnancy and lactation, endogenous depression, allergy, liver conditions, and Parkinson's disease. It might interact with drugs acting on the central nervous system such as alcohol, benzodiazepines, barbiturates and anesthetics, and may potentiate the effects of hepatotoxic agents.

Evidence and safety of alternative medical systems for insomnia

Acupuncture

Acupuncture is the insertion of needles into the skin at special sites, known as points, for therapeutic or preventive purposes. In "traditional" acupuncture it is believed that the life force "qi" and the two opposing elements yin and yang govern health. The flow of qi, which is thought to circulate in 12 meridians, can, according to traditional acupuncturists, be influenced by stimulating acupuncture points along these meridians. Traditional acupuncturists make a diagnosis according to the principles of traditional Chinese medicine, treat patients on a highly individualized basis, and are convinced that most conditions are treatable by acupuncture. "Western" acupuncturists view acupuncture as being based on neurophysiological concepts and their treatments tend to be less individualized.

Evidence of effectiveness

A systematic review of acupuncture and related techniques for insomnia included seven studies with a total of 590 patients [23]. Overall (including all age groups) the review suggested that acupuncture and acupressure may help to improve sleep quality scores when compared to placebo or no treatment. However, the efficacy of acupuncture or its variants was inconsistent between studies for many sleep parameters, such as sleep onset latency, total sleep duration, and wake after sleep onset. The combined results from three studies reporting subjective insomnia improvement showed that acupuncture or its variants was not more effective than control and significant statistical heterogeneity was observed.

Two of the included RCTs were performed in elderly individuals. One compared acupressure with sham acupressure and conversation only and reported positive outcomes for acupressure on sleep quality, sleep onset latency, and total sleep duration when compared with the sham treatment [24]. The other RCT used auricular therapy comparing magnetic pearls with auricular seed therapy and auricular placebo seed therapy, all stuck to auricular points [25]. Auricular magnetic pearl therapy but not auricular seed therapy was superior to auricular placebo seed therapy in improving sleep onset latency, sleep efficiency, and sleep duration.

Safety of acupuncture

Adverse events of acupuncture are usually mild and transient and include drowsiness, bleeding, bruising and pain on needling, and aggravation of symptoms. Serious adverse events, such as pneumothorax or infections including fatalities, have been reported but are rare. Acupuncture is contraindicated in severe bleeding disorders, first trimester pregnancy, and epilepsy. Asepsis is a pre-condition and electroacupuncture may interfere with cardiac pacemakers. Special care should be taken when needling points on the thorax to avoid injury to internal organs.

Evidence and safety of mind–body interventions for insomnia

Relaxation techniques

Relaxation techniques such as progressive muscle relaxation are effective in eliciting the "relaxation response" of the autonomic nervous system, resulting in decreases in oxygen consumption, heart rate, respiration, and skeletal muscle activity and in the normalizing of blood supply to the muscles. Other relaxation techniques involve passive muscle relaxation, refocusing, breathing control, or imagery.

Evidence of effectiveness

An RCT of 89 older adults with insomnia found relaxation more effective than placebo on sleep continuity variables [26]. Improvements in wake time after onset were recorded at post-treatment but not fully sustained at follow-up. Another trial of 51 elderly adults with insomnia secondary to illness reported mixed results [27]. Home-based audiotape relaxation was superior to cognitive behavioral therapy and wait-list control in improving total sleep time and greater change than control in sleep efficiency, wake time after sleep onset, and Pittsburgh Sleep Quality Index at follow-up. General studies including patients across the age groups report superior results of relaxation over and above placebo or wait-list controls on some sleep outcomes [28]. For autogenic training, an RCT of 229 cancer patients suffering from insomnia reported positive outcomes for sleep in the autogenic training and progressive muscle relaxation groups compared to standard rehabilitation [29]. These results for autogenic training are supported by less rigorous clinical trials [30].

Safety of relaxation techniques

Relaxation therapies are almost risk-free but are contraindicated in schizophrenic or actively psychotic patients. Techniques requiring inward focusing may intensify depressed mood. Dosages of certain medications such as antihypertensive or anxiolytic drugs might need adjusting.

Yoga

Yoga is an ancient Indian practice involving postural exercises, breathing control, and meditation. The range of techniques is believed to increase the body's vital energy (prana). It leads to a relaxation response, a reduction of sympathetic drive. The totality of these measures can increase well-being.

Evidence of effectiveness

Yoga was evaluated in one randomized clinical trial of 69 older adults [31]. It improved self-reported sleep measures including a 1-hour improvement in total sleep time compared to baseline and improvements were significantly higher than in the Ayurveda and wait-list control groups. This included better subjective sleep quality, faster sleep latency, longer sleep duration, and less use of sleep medications. The results from studies of yoga's effect on sleep in cancer patients are somewhat contradictory [32].

Safety of yoga

Yoga is relatively safe if common sense is applied. Musculoskeletal injuries through overstretching joints may occur and before starting yoga older individuals should be carefully examined for severe osteoporosis, severe heart conditions, acute back pain, knee problems, sprains and fractures, etc.

Tai chi

Rooted in ancient Chinese philosophy and martial arts, tai chi is a system of movements and postures used to enhance mental and physical health. It is based on the principles of the two opposing life forces yin and yang and is influenced by Confucian and Buddhist philosophy. Ill health is viewed as an imbalance between yin and yang. It comprises of a series of postures linked by gentle and graceful movements. The slow movements between different postures that are normally held for a short period of time are physical stimuli with effects on the cardiovascular and muscular system.

Evidence of effectiveness

One RCT assessed the effects of tai chi and self-rated quality of sleep and daytime sleepiness in 118 older adults [33]. It found that compared to exercise control older adults with moderate sleep complaints can improve self-rated sleep quality through a 6-month, low- to moderate-intensity tai chi program. Tai chi participants reported significant improvements in five of the Pittsburgh Sleep Quality Index subscale scores including an improvement of self-reported sleep duration by 48 minutes.

Safety of tai chi

Adverse effects with tai chi are rare, but may include delayed-onset muscle soreness, pulled ligaments, or ankle sprains. As with yoga, older individuals should be carefully examined for severe osteoporosis, severe heart conditions, acute back pain, knee problems, sprains and fractures, etc. before practicing tai chi.

Music therapy

Music therapy is the use of music by an accredited professional to achieve individualized therapeutic goals. For insomnia mainly receptive music therapy, i.e. listening to music, is used. Sensations that accompany music therapy may activate limbic or other areas of the brain related to the reward and motivation circuitry

(limbic-cortical circuits). Secondary physiological changes and bodily reactions may follow, i.e. autoregulatory mind/body reactions such as an influence on hemispheric dominance, changes in autonomic nervous system activity, and relaxation effects on vital functions such as breathing, respiratory rate, blood pressure, and cardiac output.

Evidence of effectiveness

Sixty people aged 60–83 years with difficulty in sleeping listened to their choice among six 45-minute sedative Western or Chinese music tapes at bedtime for 3 weeks. Music resulted in significantly better sleep quality, as well as better components of sleep quality. Sleep improved weekly, indicating a cumulative dose effect [34].

Safety of music therapy

Music therapy is associated with virtually no risks.

Conclusion

CAM treatments are increasingly popular not least because they are often wrongly perceived as "natural" and therefore "harmless". Patients frequently self-prescribe CAM and a large proportion do not disclose their use to their healthcare provider. In older patients who are more likely to take a range of medications, concomitant use of herbal and other dietary supplements poses an increased risk of interactions. Patients should be specifically asked about CAM use and informed about any safety issues. In particular, use of herbal and other dietary supplements should be considered as the safety and interactions with other drugs or CAMs has not been established. Few studies of CAM have been conducted in elderly patients and data available from trials in other age groups need to be applied with caution. CAM providers should have experience in treating the elderly and carefully consider their special needs and particular risks.

A range of CAM modalities are recommended for insomnia but few show evidence of effectiveness from rigorous clinical trials. Positive evidence of effectiveness exists for relaxation techniques, which also have a good safety record. Although only two trials are available specifically for older adults, relaxation techniques might be worth trying in this population.

Inconclusive evidence exists for a range of CAM modalities. For yoga, tai chi, and music therapy the evidence is encouraging yet limited as only very few studies are available. Although these therapies are not associated with any serious risks, no firm recommendations for their use in insomnia can be made at present.

Acupuncture may improve sleep quality scores and is relatively safe. However, as its efficacy is inconsistent for many sleep parameters, no firm recommendations can be made.

Melatonin is generally safe if used in the short term and at recommended doses. For primary sleep disorder evidence from rigorous trials suggests that melatonin may be of limited clinical use. For secondary sleep disorders or sleep disorders accompanying sleep restriction there is no evidence that it is effective. In selected elderly insomniacs low doses of melatonin may improve initial sleep quality and might be a useful treatment in this group of patients.

The use of valerian and kava for insomnia is not supported by evidence of effectiveness from rigorous trials. While valerian seems relatively safe, kava has been associated with risks, most notably hepatotoxicity, and its use for insomnia should therefore be discouraged.

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Part 4
Chapter
39

Treatment of sleep disorders in the elderly

Therapeutic benefits of napping in the elderly

Patricia J. Murphy and Scott S. Campbell

I usually take a two hour nap from one to four.

Yogi Berra

Introduction

Siesta cultures embrace an interval of daytime sleep, and many sleep researchers have argued that a mid-day nap can improve mood, alertness, and waking function [1]. Indeed, a study of elderly residents in the Okinawan village of Ogimi, called "the Prefecture of Longevity," cited the practice of taking a daily nap as equally important for good health and sleep as eating fish and thrice-weekly exercise [2]. Nonetheless, many proponents of sleep hygiene for individuals with insomnia have fostered the widespread impression that napping is to be avoided because it is detrimental to one's night-time sleep [3, 4]. In addition, some epidemiological studies have found an association between frequent daytime napping and increased risk of morbidity, mortality, and dementia [5, 6, 7]. As a result, there is much confusing and, to some extent, misleading information about the potential therapeutic benefits of napping in the elderly.

Important questions include whether there are any substantial benefits to napping, in terms of health, well-being, and productivity. Are naps associated with any side effects? Can napping even be considered a prescription for sleep difficulties? If yes, which types of sleep problems might be ameliorated with nap therapy? What would be the parameters of a nap strategy – how long, how frequently, and at what time of day should an elderly person take a nap? Before evaluating the evidence for answers to these questions, there must first be consideration of what is meant by "naps" and "napping" within a therapeutic context.

Defining therapeutic naps

Prophylactic versus appetitive versus replacement naps. A prophylactic nap can be defined as a period of sleep obtained prior to, and in anticipation of, a (usually prolonged) period of subsequent wakefulness. There is a relatively large literature describing the effects of prophylactic naps on behavioral, physiological, and psychological measures. Some groups that have been shown to benefit from prophylactic naps are truck drivers who nap prior to a long-haul drive, medical residents who nap in the middle of a 36-hour shift, and rotating shift workers who sleep in the evening prior to working the graveyard shift.

Although taken for strategic reasons, prophylactic naps differ from the types of naps we are concerned with here, primarily because their purpose is different from a therapeutic nap. Rather, daytime naps designed to address sleep disturbances in elderly persons may more appropriately be considered "appetitive" naps or "replacement" naps. Appetitive naps have been characterized as intentional naps that do not necessarily fulfill a physiological need for sleep, but may provide psychological benefits to the napper [8]. Replacement naps, on the other hand, are characterized as daytime sleep periods taken to make up for previous sleep loss, in response to fatigue or sleepiness [8]. It is likely that the widely observed increase in napping in the elderly reflects, in part, both an increased opportunity to nap (e.g. appetitive napping) and a response to the age-related disruption of night-time sleep (i.e. replacement napping).

Intended versus unintended naps. There is a psychological difference, and likely a physiological difference, between the passive "dozing off" and the active "taking a nap." When one intends to obtain sleep, one typically prepares his or her environment, making it conducive to sleep. An unintended nap, on the other hand, is not prepared for in the same manner as an intended nap; the napper is less aware that he or she is going to fall asleep. There is certainly some overlap between intended and unintended naps – as when you know that if you sit in a chair to read the newspaper in the afternoon, you are likely to doze off. But in evaluating whether naps confer therapeutic benefits, less

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relevant are studies in which self-reports of unintended naps are measured, compared with investigations in which effects of intended, planned naps are examined. Studies in which daytime sleep periods are prescribed, and analyses are directed at the effects of such naps, are likely to provide the most solid evidence about the therapeutic value of naps.

While there is a rich and lively literature concerning whether naps are associated with health, mortality, or other individual characteristics, these analyses are generally epidemiological in nature, often concerned with identifying factors associated with those who nap. As well, these studies have mostly used self-reports of naps, and rarely distinguish between intended and unintended naps. As such, this literature is only tangentially related to the question of whether active, intended napping is a viable therapeutic strategy. Nonetheless, to the extent that describing characteristics of elderly habitual nappers versus non-nappers contributes to the evaluation of naps as a viable therapy, relevant information from such studies is incorporated below.

For the current purposes, then, naps are defined as intentional intervals of sleep that occur during the daytime hours, and not in preparation for a subsequent period of sustained wakefulness. "Napping" is conceptualized herein as a strategy, or therapy, akin to a sleep aid, and most similar to other behavioral approaches that potentially affect sleep (e.g. meditation, progressive muscle relaxation). The following reviews what is known about the benefits and drawbacks of therapeutic naps in the elderly.

The need for naps in the elderly

Nearly half of all individuals over the age of 65 complain of chronic nocturnal sleep disturbance [9, 10, 11]. It should be emphasized that although sleep problems are typically more severe in elderly individuals with co-morbid medical or psychiatric burden, even otherwise healthy elderly individuals report significant sleep disturbance [12]. Both laboratory- and home-based studies using objective measures such as polysomnography and actigraphy confirm these subjective sleep complaints [13, 14, 15]. On average, when compared to younger subjects, older individuals obtain almost 2 hours less sleep per night [16, 17, 18]. Whether this reduced sleep amount reflects a decreased sleep need, a reduced capacity for sleep, or a combination of the two, remains an open question that is beyond the scope of this chapter. But it is clear that many older individuals report insufficient sleep amounts, and desire to obtain more sleep.

Additional sleep is unlikely to accrue by extending sleep into the morning hours, given that the type of insomnia most commonly experienced by older individuals is sleep maintenance insomnia. The ability to initiate sleep at the beginning of the night does not appear to be substantially affected by age, but an interaction between age-associated changes in the homeostatic pressure for sleep and the circadian regulation of sleep timing conspire to make obtaining sleep in the morning hours difficult for many older persons [19]. In addition, the fragmented and shallower sleep that typically accompanies aging decreases the amount of sleep actually obtained during the nocturnal sleep period [19, 20]. These age-related changes are often exacerbated in older individuals with medical or psychiatric co-morbidity.

Both objectively measured and self-rated sleep quality have been associated with decreased daytime alertness, poorer mood, and a decline in waking performance in the elderly. Thus, it is generally acknowledged that improved alertness, mood, and performance would accompany any significant increase in the amount of sleep obtained. But given that the capacity for night-time sleep may be physiologically limited in many elderly individuals, an alternative means of increasing 24-hour sleep amounts is to take advantage of the biological propensity to nap during the day.

Napping as a biological rhythm

Like every other animal in which circadian rest–activity patterns have been studied, humans exhibit a propensity for sleep during approximately the middle of the 24-hour day. Evidence that napping is an integral component of the human sleep–wake system comes from many sources. In toddlers, the afternoon nap is retained long after the typical morning nap is given up. Siesta cultures promote a period of rest in the afternoon hours after lunch, often officially closing businesses between approximately 13:00 and 16:00.

Laboratory studies also strongly support the notion that humans have a biological tendency to nap. Even well-rested individuals report a significant increase in subjective sleepiness and a corresponding decrease in alertness during the afternoon, accompanied by shorter sleep onset latencies during this time [21, 22].

When behavioral alternatives to sleep are limited, as in our group's studies of sleep under bedrest or disentrainment conditions, a second preferred phase

position for sleep occurs just prior to the maximum of the body temperature rhythm, coinciding with mid-day [16, 23]. Importantly, this tendency to nap is retained in aging individuals. Although there is substantial variability in the timing and duration of daytime sleep episodes in older subjects, there appears to be no significant reduction in the capacity for daytime sleep in aging. In our studies, both older and younger subjects obtained more than 2 hours of their 24-hour sleep quota during the daytime hours.

These lines of evidence suggest that perhaps the reduced night-time sleep amounts that are observed in aging, and that are associated with reduced daytime waking function, could be counteracted by supplementing night-time sleep with a daytime nap. Although this strategy has rarely been examined in aging individuals, the available results support this notion.

Effects of naps on sleepiness/alertness and waking function

The potential value of daytime naps, in terms of improved waking function, has been demonstrated in a number of studies. Such studies using healthy young adults have found overwhelmingly that napping leads to enhanced cognitive and psychomotor performance [1, 24, 25, 26, 27, 28]. This is the case for both appetitive and replacement naps.

Fewer studies have examined the effects of napping on the daytime waking function of older subjects, and results have been less consistent. A rigorous and detailed study by Tamaki *et al.* [29] compared an afternoon nap versus rest interval on mood, neurobehavioral performance, and EEG indicators of alertness in 10 healthy elderly habitual nappers. In the nap condition, subjects were permitted 30 minutes of sleep with the nap opportunity initiated at 13:00, while in the rest interval subjects watched a video from 13:00 to 13:45. Relative to the rest condition, post-nap subjective mood, reaction time and accuracy on a visual detection task, and EEG theta power were higher. It is of note that the 10 subjects included in this study napped at least three times per week habitually, were screened to have a positive attitude towards napping (i.e. reported feeling refreshed after a nap), and were free from any sleep complaints.

Whether regular afternoon napping improves waking function in elderly subjects with sleep problems was investigated by the same group [30, 31] in a study examining the effects on evening alertness of a 4-week intervention combining short naps and moderate intensity exercise. Eleven elderly subjects with chronic sleep difficulties (that were unrelated to medical illness) napped each day for 30 minutes in the interval from 13:00 to 15:00, and exercised at 17:00 each evening. Instances of nodding off in the hours between exercise and bedtime decreased from an average of 39 minutes pre-intervention to 11 minutes post-intervention. Scores on the physical health domain of the General Health Questionnaire vary significantly from 5.6 to 1.6, with 91% of the subjects reporting an improvement following the month-long nap and exercise regimen.

A study comparing a nap versus a rest interval in aging subjects was recently completed in our laboratory [32]. Older individuals, approximately half of whom had chronic sleep complaints, were given the opportunity to nap, or remained sedentary (and were not allowed to sleep) from 14:00 to 16:00, in a within-subjects cross-over design. Neurobehavioral performance on a computerized battery of tasks was assessed prior to the nap, 1 and 3 hours after the nap, and throughout the following day. Not only was performance on several tasks significantly better in the post-nap relative to post-sedentary hours, but significantly better performance was also observed on three of the four tasks the following day. In addition, we found significant correlations between parameters of the nap (duration, amount of slow wave sleep obtained) and performance measures in the 3 hours following the nap and throughout the next day. Next-day performance was related only to nap measures, and unrelated to night sleep, suggesting that the improved performance was a specific carryover effect of the previous day's nap. Further, in no case – not even on a single time trial – was post-nap performance lower than post-sedentary. These results strongly suggest that a single afternoon nap, even if relatively long, has restorative effects that do not accompany afternoon rest without sleep.

In contrast, another study found no effects on several performance tasks following 17 consecutive days of "siesta" naps [33]. Nine healthy elderly individuals without sleep complaints either attempted to nap each day from 13:30 to15:00 or were encouraged to be active during that same interval for 14 days while living at home, followed by a 3-day laboratory stay during which sleep, performance, and alertness were assessed. Each subject underwent both nap and

no-nap conditions. Evening alertness measured in the laboratory, using a sleep onset latency trial plus visual analog scales, was significantly higher following the nap than following no nap. However, none of the cognitive performance tasks differed between conditions. In that study, the nap in the laboratory did not significantly supplement the amount of sleep actually obtained per 24 hours when the daytime nap and night-time sleep amounts were combined. It may be that the amount of sleep added to the daily sleep quota by a nap is an important aspect of a "successful" nap strategy – that only if night-time sleep is sufficiently supplemented by a daytime nap is enhancement of waking function likely to result.

Effects of naps on night-time sleep

Demonstrated positive effects of napping on waking function notwithstanding, some advocates of the use of sleep hygiene to alleviate sleep problems have cautioned against napping, based on the assumption that a daytime nap would diminish the quality of subsequent night-time sleep (e.g. [3, 4]). Although this view has been tempered somewhat in recent years, particularly with respect to older individuals, the popular notion persists that napping can have a negative impact on subsequent night-time sleep. Yet, there is little empirical evidence to support the view. On the contrary, a majority of studies that have examined the issue have reported no significant negative impact of naps on night-time sleep (e.g. [17, 26, 34, 35]), or any differences in night-time sleep between habitual nappers and non-nappers (e.g. [17, 35, 36, 37]).

In elderly subjects, examination of both acute effects of afternoon naps on night-time sleep (i.e. single nap) and effects of longer-term nap regimens (i.e. weeks of daily naps) support the notion that afternoon sleep does not substantially alter sleep parameters on the subsequent night. For example, in the study by Tanaka and colleagues [30] that assessed the effects of a month of naps and evening exercise, sleep was recorded by actigraphy for 1 week each prior to and following the intervention. In these healthy older subjects, wake time after sleep onset was significantly decreased from 83 to 28 minutes from pre to post, and sleep efficiency significantly increased from 74.8% to 89.6%. Indeed, the combination of naps and exercise promoted consolidation of sleep at night, although whether one of the treatments was primarily responsible for this result could not be determined.

In our laboratory study comparing a nap versus sedentary interval, sleep was recorded polygraphically during both the nap and on the subsequent night, as well as on the night following the sedentary interval [32]. There were no significant differences between nap and sedentary conditions in any sleep measure from that night-time sleep period, with the exception of a longer sleep onset latency on the post-nap night. It should be emphasized that the difference in sleep onset latency was an average of 6 minutes (post-sedentary 15.5 minutes vs. post-nap 21.8 minutes), an increase of questionable clinical significance, given that a 22-minute sleep onset latency is well within the normal range for these older individuals [9, 20, 38]. Other night-time sleep measures were unaffected by the nap, including total sleep time, sleep efficiency, and percentage of slow wave sleep.

Perhaps more importantly, the lack of any major impact of naps on night-time sleep resulted in a significant increase in 24-hour sleep amounts when compared to the sedentary condition. Average total sleep time increased by over an hour in the nap condition (to 7.4 hours), approaching that typically reported by healthy young adults. Indeed, the addition of a nap to night-time sleep made the older subject's minutes and proportion of REM and slow wave sleep comparable to that observed in healthy young subjects.

Whether the lack of effects of a nap on night-time sleep are sustained with the adoption of a daily siesta regimen was one focus of the study by Monk and colleagues [33]. Actigraphy data and subjective sleep quality rating scales from the 14 days at home were compared across nap and no-nap conditions. No differences in night-time sleep parameters across conditions were noted; a daily nap simply had no effects on night sleep at home. In the laboratory, however, polygraphic sleep measures indicated modest but statistically reliable reductions in sleep efficiency (76.9% post-no nap vs. 74.5% post-nap) and total sleep time (366 minutes post-no nap vs. 318 minutes post-nap) after the 14-day nap regimen compared to the control condition. The authors make it clear that their study was inconclusive with respect to the influence of napping on nocturnal sleep quality, pointing out that subjects did not themselves rate their sleep quality differently across conditions, despite the polygraphic evidence that sleep time was decreased.

Tamaki *et al.* [29] also examined several questions relating to the potential impact of afternoon napping on night-time sleep. In addition, from a different,

important perspective, they questioned whether the previous night's sleep had any influence on a subsequent afternoon nap. Actigraphy records obtained continuously for about 2 weeks were analyzed by comparing night sleep prior to days with versus without naps, and night sleep following days with versus without naps. In light of findings from young subjects that replacement naps are often taken on days after a poor night's sleep [39], the authors expected differences between pre-nap and pre-no nap nights. This was not the case. There were no differences in actigraphy-based or self-reported sleep measures on nights before subjects took a nap at home versus nights that were not followed by a nap. The authors suggest, therefore, that these older subjects were taking "appetitive" rather than "replacement" naps. Their analyses also confirmed a lack of any effects of napping on the subsequent nocturnal sleep period; there were no differences in actigraphy-derived night sleep measures on nights that followed a nap versus those that did not.

In summary, the bulk of available evidence suggests that napping in the afternoon hours in elderly subjects with or without sleep complaints may have beneficial effects on waking function, and is not likely to disrupt night-time sleep. Nonetheless, potential drawbacks, or contraindications, to daily napping could deter the introduction of napping therapy in elderly individuals. Such contraindications might include sleep inertia, altered cardiac functioning during or following daytime sleep, or in some types of insomnia, amplification of night-time sleep problems. What is known of these nap-related side effects is described next.

Potential contraindications to therapeutic napping

Sleep inertia

Sleep inertia is a physiological phenomenon that occurs after awakening, characterized by subjective grogginess and reduced motor strength and coordination. The phenomenon has been somewhat well characterized following "naps" during the night-time hours, and also following a normal period of nocturnal sleep. But, only rarely has nap inertia following daytime naps been assessed, and even then, such naps have most often been taken in the middle of a period of sleep deprivation.

Studies of sleep inertia have generally indicated that its severity is greatest upon awakening from slow wave sleep, in which case the impairment may last for 20–30 minutes. Perhaps surprisingly, the time of day of awakening does not seem to be a factor; there appears to be no circadian rhythm of sleep inertia. For example, Naitoh and colleagues found that 20-minute naps initiated at varying times of day during a sleep deprivation period resulted in similar duration and magnitude of performance impairment, regardless of when the nap was taken [40]. It is also widely reported that the severity of sleep inertia following naps that are taken in the midst of sleep deprivation is more influenced by the duration of pre-nap wakefulness than by the nap duration or sleep stage upon awakening. In other words, sleep inertia following a nap embedded within a period of prolonged wakefulness is likely to be more severe than morning inertia following a normal night of sleep. Whether a planned daytime nap, which typically occurs after 6–8 hours of wakefulness, would result in inertia that is comparable to or more severe than normal morning inertia remains a matter of speculation, since we could find no report that directly compared the magnitude of post-night and post-nap sleep inertia.

The few studies that have assessed daytime nap inertia have reported either no impairment (following naps of up to 20 minutes' duration) or a quite brief duration of impairment (following 30-minute naps) [27, 41]. Tanaka and colleagues examined the issue in older subjects, and found that mood improved within 3 minutes after a 30-minute nap. Although they did not assess performance or EEG indicators of alertness until approximately 15 minutes post-nap, they found that both measures had returned to pre-nap levels by this time. All of their subjects were awakened from either EEG stage 1 or stage 2 sleep, rather than slow wave sleep.

In our study of a 2-hour nap versus sedentary period, a handful of subjects were awakened from deeper sleep stages. For the group, neurobehavioral performance was not impaired on the post-nap trial, and the few subjects who terminated the nap from SWS or REM did not differ from those who were awakened from lighter sleep stages [32]. However, the assessment occurred 60 minutes following the nap's termination, leaving open the possibility that significant inertia could have been present following this long nap.

Sleep inertia, and specifically nap inertia, might differ in young versus elderly individuals, given the age-related decline in slow wave sleep. Because of this, the probability is less, even if a nap is long, that an

older person will awaken or be awakened from slow wave sleep. Also, the fragmented and more shallow sleep of older individuals could conceivably be protective against nap inertia (e.g. do they exhibit an easier transition to full wakefulness?). On the other hand, nap inertia could cause more impairment in persons whose motor dexterity is already reduced by normal age-associated changes. In any case, inertia following daytime naps in older individuals has not been assessed sufficiently to permit firm conclusions. Despite this, recommendations concerning the utility of naps often assert that nap inertia is a "risk," and make the assumption that it will be worse in the elderly [42]. Yet, it remains an open question whether a daytime nap, taken between normal night sleep periods, is associated with an interval of increased confusion and decreased motor co-ordination, and whether such nap inertia differentially affects elderly individuals.

Cardiac function and daytime sleep

The view that daytime sleep may be associated with a higher risk for cardiovascular events is derived in part from epidemiological studies that have associated napping with risk factors for heart disease [6, 43]. However, as with the body of literature demonstrating relationships between napping and mortality, or napping and other forms of morbidity, it must be emphasized that the direction of such relationships are unknown. That is, it remains unclear whether those who take long, frequent naps have pre-existing heart conditions, or whether the napping behavior itself leads to cardiovascular problems. Also in this vein, some of these same studies have found associations between taking short naps and decreased risks for Alzheimer's disease and coronary heart disease [43, 44], resulting in the suggestion that short naps are protective against these conditions [45]. Yet, whether regular short nappers are those with other healthy lifestyle factors or whether the naps themselves are protective is not known. In any event, the discussion of nap benefits and drawbacks from such studies are peripheral to determining the potential effectiveness of nap therapy in the elderly.

Perhaps more relevant to the quest are several lines of evidence describing cardiac function during sleep, during arousals, and upon morning awakening. For example, there is a well-documented increase in heart attacks [46, 47] and stroke [48] during the early morning hours. The phenomenon has been suggested as relating to the circadian peak in blood pressure at that time of day [49, 50], to sympathetic activation during REM sleep [51], and to ventricular fibrillation and increased heart rate upon awakening [52, 53]. Also, blood pressure "dipping," a term that describes the decrease in blood pressure between wake and sleep, has been associated with the risk for ischemia and myocardial infarction. Individuals who exhibit reduced blood pressure dipping (i.e. less change between wake and sleep) appear to be at higher risk for cardiac events during sleep, and for excessive surge in blood pressure [49] during short arousals and upon awakening. Importantly, these risks are exacerbated in individuals with sleep apnea, in whom chronic hypoxia often results in compromised cardiovascular function [54].

Although studies of ambulatory blood pressure that have investigated "dipping" and cardiac function during sleep have included daytime sleep in their analyses, only a few have separated nap sleep from nocturnal sleep, or specifically analyzed cardiac function during and following daytime sleep. In one pertinent study, Bursztyn and colleagues compared ambulatory blood pressure and heart rate measured 1 hour after night sleep with that measured 1 hour after daytime sleep in 156 subjects (mean age=55 years) who napped at self-selected times [55]. Because heart rate was, as expected, higher during the day than the night, there was a significantly reduced change in heart rate upon awakening from the nap. Blood pressure was similar following night and nap sleep. The authors concluded "… therefore, that the siesta is safe …" [55] but limited this conclusion to the potential for acute ischemia in these mostly middle-aged, generally hypertensive patients.

We could find no studies that examined whether observed sleep stage-dependent changes in sympathetic activation are confined to nocturnal sleep or generalize to daytime REM and non-REM sleep. There is still much to learn about cardiac function and daytime sleep before the assumption that what occurs during nocturnal sleep will pertain to daytime sleep can be validated. At this point, it seems prudent to screen for heart disease and/or sleep apnea before nap therapy is deemed a suitable treatment.

Caveats and remaining questions

There remain several uncertainties about parameters of a putative nap therapy that will require additional research before napping can be implemented as a viable

behavioral approach for enhancing sleep and wakefulness in the elderly.

Ability to nap

Given the fact that aging is often associated with a decline in night-time sleep quality, one may question whether older subjects are able to nap for a sufficient duration to make a difference to the amount of sleep they obtain per 24 hours. In our laboratory study, all of the 32 subjects were able to fall asleep during the nap opportunity from 14:00 to 16:00, but nap durations varied widely, from 11.5 to 108.5 minutes (group average=81 ± 26 minutes). Perhaps unfortunately, we also found a significant correlation between pre-nap night sleep duration and nap duration, such that short night sleepers were short nap sleepers, and vice versa. As such, it may be that the very individuals who would benefit most from a daytime nap are those who have the greatest difficulty napping.

Like most interventions for sleep loss, a napping regimen will almost certainly not prove to be useful for everyone. Both common experience and the scientific literature indicate that there are "nappers" and "non-nappers" just as there are long- and short-sleepers and morning and evening types. Whether a non-napper can learn to be a napper is not clear. Accomplishing this "conversion" would likely require some persons to adjust not only their daytime behavioral routines, but their beliefs about napping as well.

Acceptance and compliance

For many, napping is associated with indolence or senility. Moreover, many people continue to hold the belief that an afternoon nap will disturb their night-time sleep. Such views may militate against the acceptance of a napping regimen. Yet, the finding by Monk and co-workers of good compliance during their 17-day protocol provides some evidence that a napping schedule can be successfully implemented [33]. The majority of participants in their study were habitual non-nappers, but all were able to integrate a nap into their days for 2 consecutive weeks. In a follow-up to our previous nap versus sedentary study, we have obtained preliminary evidence to suggest that a daily 2-hour nap for a month may be too much of a lifestyle interruption. Subjects assigned to our 45-minute nap condition have been more compliant than those in the 2-hour condition. Perhaps limiting nap durations would improve adoption of nap therapy, as several studies have indicated that even in habitual non-nappers, there was wide acceptance of shorter daily naps. While these investigations usually found that a 20–30 minute nap enhanced waking function, the question of what constitutes optimal nap duration for an elderly individual remains.

Optimal nap duration

How long is long enough to promote wakefulness and enhance cognitive performance while, at the same time, reducing the likelihood of nap inertia effects and night-time sleep disturbance? We could identify no studies that have examined "power naps" specifically in elderly individuals, but the study by Tanaka and colleagues found no effects of 10- and 20-minute naps on post-nap cognitive performance. On the other hand, the report by Monk and colleagues found that despite obtaining about 1 hour of sleep per day, subjects showed no improvement in waking function (although, as mentioned, these subjects also did not significantly add to their night-time sleep amounts.) Perhaps the most sensible approach to prescribing nap duration would be to permit each individual to assess how short or long a nap makes him or her feel best, in terms of sleep inertia, subsequent function, and night-time sleep.

Optimal nap timing

At first glance, it may seem that the best time of day to nap is a clear-cut issue. There is, after all, the well-documented increase in sleep propensity during the mid-afternoon hours [22], which appears to be conserved with aging [56]. In addition, older habitual nappers also report, with remarkable consistency, that they too prefer to nap between approximately 13:00 and 16:00. Indeed, most of the nap studies described earlier utilized this evidence in their study designs, deciding that an afternoon nap was the most logical choice. As a result, there is little evidence to either refute or confirm the idea that prescribing morning or evening naps would produce therapeutic effects similar to afternoon naps.

One relevant study by Yoon and colleagues reported that evening napping was a "characteristic" of the post-menopausal women they studied [57]. More than 40% of the 436 women in their study napped regularly in the 2 hours prior to bedtime. Interestingly, the evening nappers had slightly better nocturnal sleep, as measured by actigraphy, than non-evening nappers. Thus, while it is correct to assert that afternoon naps are typical, and have been the most frequently studied,

additional research examining alternate nap timing is needed to confirm whether the afternoon is always the preferred time during which to take a therapeutic nap.

Who would benefit from therapeutic naps?

Besides otherwise healthy older individuals suffering from an age-related decline in night-time sleep quality, there are subgroups of elderly individuals for whom regular, prescribed napping may be particularly appropriate. Many elderly individuals are unwilling or contraindicated for pharmacotherapy for sleep problems, and desire behavioral options to address these sleep problems. Although other behavioral treatments, such as cognitive behavioral therapy for insomnia, have been shown to be effective in older insomniacs, this type of therapy is less of an option for those with dementia. Individuals with dementia often experience severely fragmented and short night-time sleep periods, and exhibit multiple unintended naps throughout the daytime hours. A schedule that encourages activity until a scheduled afternoon nap period may enhance post-nap cognitive functioning. For many of these persons, a positive effect on evening cognitive function could help counteract dementia-related behaviors (e.g. sundowning) that are often at their peak during this time.

Another group that might be especially suited to nap therapy is those who experience cancer-related fatigue, without night-time insomnia. Such individuals often report overwhelming daytime sleepiness, and might benefit from a routine of consolidated daytime sleep. An afternoon nap that reduces sleep pressure during the middle of the day would more directly address the nature of their sleep problem than treatments designed to target night-time sleep.

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Part 4
Chapter
40

Treatment of sleep disorders in the elderly

Effects of light on the elderly

Glenna A. Dowling and Judy Mastick

Introduction: state of the knowledge

Exposure of the eyes to light of sufficient intensity and duration at the appropriate time of day can have profound effects on the quality, duration, and timing of sleep. The effects of light on the brain are mediated by the retinohypothalamic tract with the daily light/dark (LD) cycle being the primary input for entrainment of circadian rhythms to the 24-hour day. Light is the most powerful zeitgeber (from German for "time giver") of the internal time-keeping system.

Efforts to find non-pharmacological treatments for elderly patients with sleep maintenance insomnia have led to the investigation of timed bright light therapy. This treatment is based on the assumption that age-related sleep disturbance is the consequence of alterations in the usual temporal relationship between certain circadian rhythms, for example, core body temperature and sleep [1]. The objective of light therapy is to normalize the sleep phase in relation to other rhythms. Healthy older adults face functional changes and degenerative nervous system changes that affect their circadian rhythms, adding to the need for strongly stimulating and appropriately timed light zeitgeber for entrainment.

The most recent practice parameters on the use of light therapy for treating sleep disorders were published by the American Academy of Sleep Medicine in 1999. Evidence was presented by grade and level. Citing the only two studies that met their inclusion criteria, the authors determined that bright light may be effective in the treatment of advanced sleep phase syndrome (ASPS) in older adults, appears safe, and has clinical utility for ASPS. However, they also concluded that "adequate studies are not available to provide specific recommendations; and that more work is needed in the study of aging and dementia, in which phase shifts may not be crucial elements of the clinical disorder" [1].

The Cochrane Collaboration also published a review of the literature (through January 2001) related to bright light therapy for sleep problems in adults 60 years and older. Literature involving subjects with dementia and/or depression were excluded. They found no randomized controlled trials on which to base recommendations. However, given the potential positive impact of alternative therapies compared to hypnotics in this population, the reviewers concluded that further research was justified [2]. Subsequent to the publication of the Cochrane review, results from research reports remain inconclusive about the effects of light therapy in the elderly. Although the effects of light treatment on sleep parameters are inconclusive, positive effects of light on cognition, alertness, energy, performance, and well-being have been reported [3, 4].

Circadian physiology and light

Environmental light plays a fundamental role in regulating circadian physiology [5](Table 40.1). A small percentage (0.2–0.8%) of the retina is composed of photoreceptive ganglion cells containing the photopigment melanopsin. These non-visual photoreceptors most likely work in combination with visual receptors (rods and cones) in neurons to synchronize circadian rhythms [6]. While the ganglion cells are few in number, their dendritic projections are widely dispersed and cover the entire retina [7, 8]. These ganglion cells display exquisite photosensitivity to low levels of blue light in the range of 460–485 nm [7, 9], such that blue wavelength light produces the strongest effect on regulation of pineal melatonin production and release [10]. Studies comparing blue wavelength to white light show a two-fold increase in melatonin suppression and circadian shift in response to blue light. Under ideal conditions, 8 lux of blue light can be as effective as 12 000 lux of white light [10, 11, 12].

Melanopsin in the ganglion cells absorbs light energy and triggers phototransduction resulting in physiological responses in the suprachiasmatic nucleus (SCN) via the retinohypothalamic tract. The SCN

Principles and Practice of Geriatric Sleep Medicine. ed. S.R. Pandi-Perumal, J.M. Monti, and A.A. Monjan.
Published by Cambridge University Press.

Table 40.1. Light regulation of the human circadian system

Elements of ocular physiology
• Physics of the light source
• Conscious and reflex behavior relative to the light source
• Transduction of light through the pupil and ocular media to the retina
• Photoreceptor wavelength sensitivity
• Photoreceptor distribution
• Neural ability to integrate stimuli temporally and spatially
• State of photoreceptor adaptation

projects to the pineal gland, which synthesizes and releases melatonin. It is well established that light is the primary synchronizer of the circadian timing system. The specific effect of light, however, depends on the timing, intensity, and duration of exposure to the light stimulus. Light exposure in the afternoon and evening typically phase delays the circadian clock and the onset of sleep (i.e. to a later time), whereas light exposure in the morning typically phase advances the clock (i.e. to an earlier time). Under usual circumstances, exposure to light during the day and darkness during the night promotes entrainment of the circadian clock to the 24-hour light/dark cycle.

The photosensitive ganglion cells also have direct and indirect (via the SCN) projections to brain areas implicated in the regulation of arousal [3]. The circadian process balances the homeostatic drive for sleep with the wake-promoting drive during wakefulness. Kaida *et al*. examined the effect of exposure to 30 minutes of natural bright light at lunchtime on adult worker's performance and arousal levels and found an increase in afternoon arousal levels, and a decrease in afternoon sleepiness [13]. Murphy and Campbell also found that bright light exposure improved performance but not necessarily sleep efficiency [4].

The human circadian system shows adaptive responses to "light history." The absolute levels of prior light exposure will influence the role of subsequent dim light exposure. Higher intensity prior light history dampens the magnitude of subsequent melatonin suppression by light by about 10–15% [14]. Adaptation to prior light exposure is a relatively new concept and the mechanism by which the level of ambient light and duration of exposure affect the adaptation response in humans is unknown. Clearly, day length and consequently light exposure is critical in seasonally breeding species regulating the timing of reproduction.

Numerous age-related alterations in the fidelity of the circadian timing system have been reported (e.g. [15]). Decrements in rhythm expression result in poorer overall functional status including increased cardiovascular morbidity and mortality, hypo- and hyperthermia, depression, cognitive decline, and decreased ability to re-entrain after a phase shift [16]. In general, it appears that the phase response to light in older, healthy elderly individuals is of similar magnitude to that of young adults and there is no difference between men and women [17, 18]. However, some circadian rhythms may be advanced in older compared to younger subjects. For example, Kripke *et al*. found the onset of melatonin secretion to be phase advanced in older compared to younger subjects. Melatonin secretion offset was proportionately less advanced than onset resulting in longer melatonin secretion duration in older participants. These investigators hypothesized that prolonged melatonin secretion duration might tend to increase phase responsiveness of older subjects to light, which might possibly compensate for reduced ophthalmic light transmission [19]. Phase advances of the early morning rise of the core body temperature rhythm and habitual sleep period, and changes in phase relationships between these rhythms, result in decreased ability of older adults to maintain sleep in the morning and increased complaints of sleep-maintenance insomnia.

Aging is also associated with decreased exposure to light and decreased transmission of light to the retina due to changes in the anterior chamber of the eyes. The density of the retinal ganglion and epithelial cells decrease with age, presumably due to oxidative processes [16, 20]. There is also evidence that in certain disease processes (e.g. Alzheimer's disease) SCN neuronal activity disruption occurs at younger ages and is more pronounced than in normal aging. These disease-related changes result in a weaker expression of rhythm amplitudes and increased inter-individual variability.

Ocular light transmission

The amount of light entering the visual system is regulated by the pupil. Weakening of the muscles in the iris results in decreased pupil diameter with aging, such that a 60-year old pupil is about one-third the size of a 20-year-old pupil. A smaller pupil allows less light into the eye, reducing retinal illuminance by about a

factor of 2 in the eye of a 70-year-old compared to a young adult [21]. The aged pupil reaction to light is also slowed, which makes adapting to changing light environments difficult [22].

As light enters the eye through the cornea, it is focused on the retina by the lens. Corneal curvature increases slightly with age, and reduced corneal density and clarity scatter light as it passes through to the retina [21].

The lens becomes less pliable, more conical in shape, and continues to grow such that its thickness increases 28% by age 70. The lens substance changes from clear to yellow, and this, combined with increased thickness, results in selective absorption of shorter wavelengths of light, particularly blue light. The thicker, yellowing lens also encourages scattering of shorter light wavelengths and creates an effect of veiling glare that further reduces retinal illumination and contrast sensitivity.

These age-related ocular structural changes produce changes in the photobiology of circadian rhythms. Three times as much environmental light is required to produce the same amount of retinal illuminance in an older compared to a younger person. Furthermore, 85% of older adults evidence some sort of eye pathology with the most common diagnoses being cataracts, glaucoma, and macular degeneration. All of these disorders negatively affect ocular light transmission [22]. By the ninth decade of life, 68% of individuals have cataracts [23]. Cataract removal surgery and subsequent lens implantation provide for post-operative light transmittance comparable to that in young adults [22].

Environmental light exposure

Light is typically measured in lux with 1 lux being the illumination produced by one candle at 1 m from a surface. A full moon produces 1 lux of light, office light ranges from 50 to 500 lux, a rainy or cloudy day outdoors ranges from 500 to 2000 lux, and full sunlight at noon measures 10 000 lux in a horizontal gaze direction [24]. The natural photoperiod, defined as the time from just after sunrise to just after sunset, also varies in intensity depending on weather, season, latitude, and gaze direction. Historically, humans spent much of the day outdoors, but since the industrial revolution and invention of the incandescent light bulb, people spend much less time exposed to outdoor light and much more time indoors exposed to generally overall lower levels of illumination. A study of natural light exposure in young adults living in southern California revealed high inter-individual variability depending on the amount of time spent outdoors. People who work indoors in spaces without windows typically spend only 23 minutes (their commute time) in light levels of sufficient intensity for optimal circadian synchronization (2000 lux) [25]. One study reported that middle-aged people spent only 13% of a 24-hour day (3.2 hours) exposed to light greater than 100 lux, with only 58 minutes in light greater than 1000 lux, and 23 minutes in light greater than 2500 lux [26].

Light exposure also decreases with increasing age, and this decrease worsens as health declines resulting in even more time being spent indoors. Only 50% of healthy subjects aged 79–96 years had outdoor light exposure greater than 3 hours during the course of a week [27]. Subjects with dementia only spent about 30 minutes in light greater than 2000 lux compared to healthy elderly who spent about 1 h in light greater than 2000 lux [28]. Institutionalized patients, aged 60–100 years, without dementia or with mild to moderate dementia spent a median of 9 minutes exposed to light greater than 1000 lux, whereas those with severe dementia spent only 1 minute above 1000 lux [29]. Insufficient contrast between day light exposure and night light exposure has also been reported to decrease the strength of the day–night rhythm in some nursing home patients [30].

Types of light therapy

While the appropriate intensity, duration, and timing of exposure to light has not been established, research results indicate that bright light therapy may be an effective treatment strategy for a variety of sleep-related disruptions.

Light boxes

There are many commercially available light boxes. In general, these boxes yield a maximum of 10 000 lux light with the patient seated about 1 foot from the screen. With the direction of gaze down towards the work surface, this level of illumination is generally well tolerated. There is some evidence that positioning the light source above eye level so that the majority of the light falls on the lower portion of the retina, where there is a proportionately higher concentration of ganglion cells, may be more effective, for example, in suppression of melatonin [31].

Increased ambient light

The circadian system can respond to low levels of light and variations of light intensity throughout the

24-hour day. An increase in ambient light has been tested in group living environments. Van Someren *et al.* increased the ambient lighting in a group home for elderly patients with dementia for 1 week and found increased stability in the rest–activity rhythm [32]. In a residential facility, Sloane *et al.* tested the effects of exposure to morning, evening, or all-day light for 3 weeks. They found night-time sleep improved for people with dementia significantly in the morning and all-day light exposure groups [33].

Dawn–dusk simulators

These computer-controlled lighting devices deliver light that mimics the gradual transitions found outdoors in spring or summer. The light is relatively dim and is delivered during the end of the major sleep episode when the eyes are adapted to the dark, and the circadian timing system is most sensitive to phase advances. Dumont and Beaulieu suggest that this produces a more pronounced contrast between day and night and seems to be a promising approach, particularly with institutionalized patients [34]. Dawn simulators have also been studied for treating seasonal affective disorder (SAD) [35] and in the nursing home for treating rest–activity disruption in patients with dementia [36].

Wavelength specific therapy

Data on the effect of blue wavelength light on circadian rhythms in people with dementia are limited to one small pilot study in subjects with Alzheimer's disease (AD). After blue light exposure, subjects "slept better," experienced a shift (advancement) of peak activity to midday and an increase in the ratio of activities during the day to those at night, indicating consolidation of the rest–activity rhythm [37].

Safety and side effects of light therapy

Light therapy appears to have a good safety record. However, cumulative photo-induced retinal changes may take decades to reach a pathological threshold. Without longitudinal studies it is impossible to determine, for certain, the effects of light treatment versus age-related degenerative changes [38]. Retinal epithelial cells and possibly photoreceptors are particularly susceptible to damage from short, blue wavelength light, depending on duration and intensity, with the "blue light hazard" being at approximately 450 nm. Older people, particularly those with macular degeneration, are more susceptible to damage by blue wavelength light. Light in the ultraviolet range (280–400 nm) can also be damaging and should be avoided. The diffusion filters used in commonly available light boxes vary widely and consumers should carefully examine manufacturer -provided transmission curves in comparison with published safety standards.

A thorough ophthalmological examination including assessment for any eye complaints, retinal or corneal abnormality, glaucoma, cataracts, intraocular (IO) lens implants and type, current medications with identification of medications that increase photosensitivity, and non-ocular conditions are recommended prior to starting light therapy. Patients with retinal diseases such as diabetic retinopathy, macular degeneration, or retinitis pigmentosa should not receive bright light therapy. Patients with glaucoma and clear intraocular lens implants should be closely monitored.

Most of the minor side effects associated with bright light therapy are attributable to intensity and duration of the exposure. Common side effects include headache, nausea, jitteriness, and eye irritation. These symptoms usually resolve within 2–5 days or with dose reduction. Less common side effects include blurred vision, seeing spots, photophobia, and perceptual glare. Insomnia and hyperactivity can occur with light exposure that is too late in the day. Premature awakening and difficulty returning to sleep can occur if light exposure is too early in the day. Little data is available that specifically relates to the older adult.

While light has been investigated as a treatment for agitated behaviors (e.g. [36, 39]) little work has been done on potential adverse effects of bright light and none on blue light on behavior in patients with dementia. There is some evidence that blue light increases alertness and, in subjects with already elevated levels of agitation, may increase "emotional tension"[40]. In our own work, we found small, but statistically significant, increases in agitation/aggression behaviors after morning and afternoon light exposure [41]. Agitated behaviors in patients with dementia may indicate "discontent" [42].

Conditions for which light therapy may be beneficial

There are no compelling data available pertaining specifically to the duration and treatment of light therapy for older adults. Little data exist on the carry-over effects of bright light exposure and patients may relapse once light therapy is discontinued. Further research is needed.

Light therapy has been tested as a treatment for the following conditions in adults:

- *Insomnia*. The most recent Cochrane Collaborative report found no trials on which to base effectiveness of light therapy for insomnia, however promising results with bright light therapy in other populations with problems of sleep timing indicate that further research seems justifiable [2].
- *Delayed sleep phase syndrome.* In delayed sleep phase syndrome, the major sleep episode is delayed (later) in relation to the desired clock time for sleep. The result is prolonged sleep onset latency and difficulty waking at the desired time. Morning light treatment is recommended for advancing the circadian rhythm to a more acceptable time. A typical treatment recommendation is 2000–2500 lux exposure from 06:00 to 09:00 and optionally wearing dark goggles from 16:00 to dusk [1].
- *Advanced sleep phase syndrome.* In advanced sleep phase syndrome, the major sleep episode is advanced (earlier) in relation to the diurnal circadian clock time for sleep. The result is complaints of being unable to stay awake in the evening and waking up too early. Evening light treatment is recommended for delaying the circadian rhythm to a more socially acceptable time. A typical treatment recommendation is 2500 lux exposure for 4 hours from 20:00 to midnight or 4000 lux for 2 or 3 hours from 20:00 or 21:00 to 23:00 [1].
- *Non-24-hour sleep–wake syndrome.* A non-24-hour syndrome is when the circadian time-keeping system's period differs from the 24-hour light/dark cycle causing patients to fall asleep at a different time each day. There are no light treatment standards or recommendations for this disorder [1].
- *Jet lag.* Jet lag is a syndrome produced by transmeridian travel. The resultant symptoms include difficulty maintaining sleep at night and daytime sleepiness in the new time zone. Symptoms typically resolve after a few days; however, older individuals require more time to adjust to the new clock time than younger adults. Light treatment has not been shown to be a consistently effective treatment [1].
- *Dementia.* The sleep pattern disruptions in dementia include frequent awakenings at night and frequent naps during the day as well as sundowning. These symptoms are among the most challenging disorders for care-givers to manage in the older, demented individual. Several studies have indicated that bright light therapy can improve the disrupted rest–activity pattern often seen in patients with dementia, but results have been inconsistent, and bright light as a treatment cannot be definitively recommended [1, 36, 43, 44].
- *Seasonal affective disorder.* Seasonal affective disorder is a mood disorder characterized by recurring episodes of major depression during particular seasons, usually beginning in autumn/winter and remitting in spring. This disorder is the most studied for intermittent use of light therapy in the community environment, although not specifically in the aged population. Specific treatment timing is dependent upon an individual's melatonin onset time, but usually light exposure is recommended for 2–3000 lux for 2 hours or 10 000 lux for 0.5 hours in the morning [1, 45].

Recommendations

Light treatment protocols include enhanced light exposure that compensate for the reduced transmission and retinal sensitivity, individual timing anchored to the circadian phase, and strategies that enhance rhythmic amplitude beyond phase shifting [35]. The current knowledge is best served in the aged population by utilizing light in order to support the natural environment light/dark cycle (see Table 40.2). The relative ease and inexpensive nature of obtaining sunlight exposure compared to special lighting equipment makes natural light exposure a practical consideration for potential therapeutic use. Proper sleep hygiene is recommended as an adjunct to light therapy [1]. Supporting strength and stability of other zeitgebers, including activities, exercise, meals, and coffee and tea breaks, may have an additive effect with the improvement in natural light exposure. Integrating chronotherapeutics with other treatment modalities may prove to be more effective than a single treatment.

Resources

The Lighting Research Center http://www.lrc.rpi.edu/programs/lightHealth/AARP/index.asp "Lighting the Way: A Key to Independence," by Mariana Gross

Table 40.2. Effective lighting for vision and circadian entrainment

Maximize difference between day and night light
Bright light during the day:
• Go outside or sit near a bright window for at least an hour in the morning
• Use light bulbs with 1000 lumens for general lighting
• Use 75–100 watt incandescent or 50 watt fluorescent for task lighting
• Increase reflective light by using torchiere style lights
• Decorate with light colors on walls, ceilings, floors
• Use adjustable task lights for detail work, and to increase contrast
Darkness at night:
• Use low lumen night lights with red light bulbs
• Don't turn on overhead lights
• Use lighted toggle wall switches
• Keep a flashlight by the bedside
Minimize glare
• Shade or cover light bulbs
• Position desk task light close to and to the side of the visual target
• Aim light away from face
• Use frosted instead of clear glass fixtures
• Choose matte finishes instead of shiny finishes
• Use blinds, shades, or curtains
Increase visual discrimination
• Paint edges of stairs, ramps, and doorways in high-contrast colors
• Use a dark placemat or tablecloth with light colored dishes
Transition light levels
• Avoid abrupt changes in light intensity
• Paint transition areas in colors, going from very light to light to dim rather than very light to dim
Improve color perception
• Use high-lumen, high-quality fluorescent bulbs
• Avoid incandescent bulbs
• Position light to eliminate shadows from light on detail work or task

Figueiro is a free, downloadable booklet that details effective lighting for various tasks in different areas in the home and how to go about implementing changes. It comes in three versions, for healthcare providers, older adults, and architects.

The Center for Environmental Therapeutics http://www.cet.org/ is a non-profit website that provides information for the public and clinicians about light therapy and seasonal affective disorder, as well as criteria for light box selection. Also available are free downloads of journal articles (see e.g. [45]). An excellent reference for phase shifting with light therapy is given in [46].

The Society for Light Treatment and Biological Rhythms (http://www.sltbr.org) is a useful resource and light box manufacturers include: Philips lighting (http://www.usa.philips.com); consumer products, personal care, light therapy; Enviro-Med (http://www.bio-light.com); and Sunbox (http://www.sunbox.com).

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Part 4
Chapter
41

Treatment of sleep disorders in the elderly

Neuroimaging of sleep in the elderly

Eric A. Nofzinger

Introduction

The aging process is associated with characteristic changes in subjective and objective sleep. This chapter reviews the brain mechanisms that may account for these changes as revealed by brain imaging studies of sleep in the elderly, including both morphological and functional neuroanatomical studies. The results reveal characteristic alterations in brain function and metabolism that relate to, and likely account for, the observed subjective and objective changes in sleep associated with aging. First, the preclinical observations of the mechanisms of sleep are reviewed, then studies of the functional neuroanatomy of sleep in mid-life, and finally, existing studies using brain imaging in relation to sleep in the elderly.

Subjective sleep is impaired in the elderly: these impairments are associated with increased morbidity and mortality

Complaints of insomnia, fragmented sleep, and poor-quality sleep are more prevalent in older adults (aged >55) than in any other age group [1]. The public health burden of these changes in subjective sleep is significant. Studies have linked these alterations to increased utilization of health services [2], increased use of sedative-hypnotics [3], reduced functional capabilities and quality of life [4], increased risk for physical illness and emotional problems or mental disorders [2], and increased likelihood of nursing home placement for ill individuals [5]. Several [5], but not all [4] epidemiological and community-based studies have reported that sleep complaints and sleep duration predict future physical health decline and all-cause mortality. Given the limitations of studying large numbers of subjects with EEG sleep methods, these large-scale studies have relied on subjective impressions of sleep that may not always correlate with objective sleep assessments [6].

EEG sleep is altered in late-life

Studies using EEG sleep measures consistently report altered sleep in older subjects. For example, Buysse *et al.* [7] compared EEG sleep among healthy elderly subjects (age >78) and young adults (20–30 years old). They reported poorer sleep consolidation (decreased time asleep, increased arousals, and minutes awake), a lower percentage of REM sleep, shorter REM latencies, and less slow wave sleep in the older group. These EEG sleep changes were consistent with poorer subjective ratings of sleep in the older group. Similar findings have been reported in other studies [8]. Deterioration in sleep efficiency has been noted to continue within elderly groups followed over time [9]. Preservation of slow wave sleep into aging has been reported in women, but not men. Reynolds *et al.* have argued that sleep, particularly sleep initiation and REM sleep, serves as a sensitive psychobiological marker of successful aging and adaptation in late-life given that age-related health declines can be predicted by these elements of EEG sleep [10]. Given recent technical developments in assessing brain function within sleep, we are now in a position to be able to clarify the underlying functional neuroanatomical basis for these observed changes in both subjective and objective sleep in the elderly that are fundamentally related to their prospects for continuing in life in good health.

Building a model of functional neuroanatomical alterations in sleep related to the aging process

A model of brain structures that may function abnormally to disrupt sleep in the elderly can be developed by reviewing the relevant literature in several domains: (1) basic physiology of sleep/wake, or behavioral state, regulation; (2) human functional neuroimaging studies during sleep; and (3) studies related to aging brain function.

Principles and Practice of Geriatric Sleep Medicine. ed. S.R. Pandi-Perumal, J.M. Monti, and A.A. Monjan.
Published by Cambridge University Press.

Sleep physiology: pre-clinical

Sleep consists of two discrete brain states, NREM and REM sleep. We will review the basic brain mechanisms underlying the global changes in behavioral state from waking, to NREM, and to REM sleep, as well as the core brain structures that play roles in the generation and modulation of these brain states.

Mechanisms underlying behavioral state changes: thalamo-cortical oscillations

The brain mechanisms related to normal behavioral state regulation have been studied extensively at the preclinical level. The work of Steriade and others [11] continues to define the brain mechanisms related to electrical oscillations in corticothalamic systems across the primary behavioral states. With respect to localizing the brain structures underlying slow wave sleep, several features are important. First, the electrical oscillations observed at the macroscopic level are the end result of electrical oscillations involving widespread thalamo-cortical neurons that are synchronized in a global fashion. Second, widespread changes in these oscillations can result from state-dependent changes in modulatory systems such as the brainstem, the hypothalamus, and the basal forebrain. Third, slow oscillations in the 1–4 Hz delta range have both cortical and thalamic components. This line of research emphasizes that rhythmic oscillations are the end result, therefore, of integrated corticothalamic circuits and modulatory structures. Changes in delta sleep, expressed most sensitively by quantitative analysis of the EEG, may therefore result from functional changes at one or more levels including the cortex, thalamus, and modulatory structures.

Mechanisms underlying behavioral state changes: core structures related to arousal

Arousal and the maintenance of an aroused state is an active process requiring the integrated activity of a series of arousal systems, which are shown diagrammatically in Figure 41.1 [12]. The central brainstem arousal system is the ascending reticular activating system (ARAS) [13]. The ARAS projects into a series of specific brainstem systems including the pontine cholinergic nuclei, midbrain raphe nuclei, and the locus coeruleus, and into a series of forebrain structures involved in arousal. These include the midline and medial thalamus with widespread cortical projections and the amygdala, which has interconnections with isocortex and with other areas involved in arousal, particularly the hypothalamus and ventral striatum. The amygdala is particularly involved with autonomic regulation and the emotional component of arousal. There are two important components of the basal forebrain-ventral striatum system [14, 15, 16, 17]. One is the cholinergic neurons of the medial septum–nucleus of the diagonal band–nucleus basalis complex which innervates the entire forebrain. The second is the nucleus accumbens–ventral striatum complex, which is involved in transmitting the arousing aspects of reinforcing stimuli. Until recently, the importance of the the hypothalamus was not fully recognized, but this is rapidly changing. First, we now appreciate that an important component of the circadian control of behavioral state is the maintenance of arousal by the circadian pacemaker, the suprachiasmatic nucleus [18]. Second, there are extensive hypothalamic projections to the isocortex, predominantly from the posterior hypothalamus. These include a newly discovered projection from a group of neurons that produce a novel peptide hypocretin. This projection is of particular interest because the hypocretin neurons project not only over the entire isocortex but to all of the arousal systems noted in Figure 41.1 including extraordinarily dense projections to locus coeruleus, raphe nuclei, pontine cholinergics, midline thalamus, nucleus basalis, and amygdala [19]. The hypocretin projection has become of particular interest because a hypocretin gene knockout produces a narcolepsy-like syndrome in mice [20] and hypocretin is below detectable levels in CSF from narcoleptics in comparison to controls [21]. The relationships between function in any of these arousal systems and the behavioral state changes in the elderly, however, are not currently known.

Neuronal basis of REM sleep: core structures involved in REM sleep generation

Evidence from a variety of approaches suggests that the laterodorsal and pedunculopontine tegmental cholinergic nuclei (LDT and PPT) in the pontine reticular formation underlie the phasic and tonic components of REM sleep. A reciprocal interaction hypothesis claims that these cholinergic nuclei become disinhibited during the entry into REM sleep by the removal of tonic inhibition from noradrenergic and serotonergic nuclei as these monoaminergic nuclei slow or become silent in the transition from NREM to REM sleep [22]. Modifications of this model now

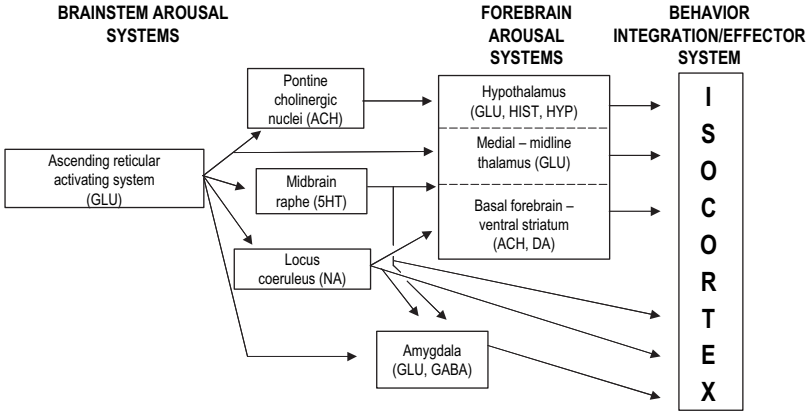


Figure 41.1. Arousal systems in the human brain (see text for description). The transmitters associated with each system are abbreviated: ACH, acetylcholine; DA, dopamine; GABA, gamma aminobutyric acid; GLU, glutamate; HIST, histamine; HYP, hypocretin; NA, noradrenaline; 5HT, serotonin.

account for the influence of additional brainstem neurotransmitter systems such as GABAergic, nitroxergic, glutamatergic, glycinergic, histaminergic, adenosinergic, dopaminergic and various peptide systems such as galanin, orexin, vasoactive intestinal polypeptide, and nerve growth factor and hormonal influences such as growth hormone releasing hormone, prolactin and corticotropin releasing factor. Ascending pathways from these brainstem reticular nuclei include a dorsal pathway innervating the thalamus and a ventral pathway innervating the basal forebrain [23]. These subsequently mediate the widespread cortical arousal characteristic of REM sleep [24]. Human brain imaging studies of REM sleep show that the ventral pathway predominates during human REM sleep in activating anterior paralimbic structures [25].

Neuronal basis of NREM sleep: core structures involved in NREM sleep generation

Preclinical studies suggest several brain structures play central roles in either the generation of sleep, or participate significantly in the expression of sleep. In general, these structures are either part of the ascending reticular activating system, a system that needs to be turned off in order for sleep to occur, or part of a distributed system that inhibits these activating brain structures. Notably, there is close spatial proximity as well as extensive interconnections between structures that serve these opposing operations. Brain structures related to the generation of NREM, or slow wave sleep, include the anterior hypothalamus, pre-optic area, basal forebrain, the lower brainstem reticular formation, the solitary tract nucleus, non-specific thalamic nuclei, the anterior hypothalamic/pre-optic area, and the basal forebrain. The mechanism by which these structures may induce sleep is thought to result from their inhibitory connections with structures noted above that promote cortical activation or via more direct inhibitory projections to the cortex.

Neuronal basis of REM sleep: forebrain structures that modulate REM sleep generation and expression

In large part, preclinical studies have focused on either the primary nuclei that generate REM sleep or that are functional in mediating the cortical arousal as it relates to either REM sleep or waking. Less information is available regarding structures that modulate activity in these centers [13]. Recent work shows that the amygdala is anatomically connected with and functionally modulates effects on the brainstem centers involved in REM sleep production [26]. Similarly, other forebrain structures such as the hypothalamus, the basal forebrain, the ventral striatum, the anterior cingulate cortex, and the ventromedial pre-frontal cortex are known to have both anatomical and functional relationships with brainstem centers thought to play a role in behavioral state regulation in addition to the primary roles they each play in cortical arousal. While it is possible that REM sleep changes in the elderly are associated with pathological changes in the core brainstem structures that generate REM sleep, it is as likely that there is age-related pathological function in forebrain structures that modulate REM sleep.

Neuronal basis of REM sleep: evidence from functional brain imaging studies

Functional brain imaging studies have shown that global cerebral metabolism, a correlate of neuronal activity,

during REM sleep is comparable to that in waking [27, 28]. Regionally, REM sleep has been reliably associated with the selective activation of limbic and paralimbic structures in the absence of lateral pre-frontal cortex activation [25, 29]. More specifically, there is a reliable activation from waking to REM sleep in a broad region of anterior cingulate cortex, the ventral striatum and basal forebrain, ventromedial and medial pre-frontal cortex, the amygdala, the pontine brainstem, and the thalamus. These findings are strikingly similar to those found in preclinical studies using either autoradiography or immediate early gene expression to define regional brain function [30]. Functionally, these structures are thought to play key roles in attention, emotion, reinforcement, and perseverative behavior. This pattern of activation has led to the use of a waking to REM sleep functional brain imaging paradigm as a probe of human limbic and paralimbic function [25, 31]. The utility of this probe for identifying functional brain alterations in mental disorders in which limbic alterations are hypothesized has been demonstrated [32]. This pattern of cerebral activation during REM sleep suggests that the alterations in electrophysiologically measured REM sleep previously found in the elderly may reflect altered function in brain structures that mediate adaptive behavior.

Neuronal basis of NREM sleep: evidence from functional brain imaging studies

Prior functional brain imaging studies of sleep that have measured absolute brain function generally support the notion that NREM sleep is a resting or less functionally active behavioral state of the brain in relation to waking and REM sleep [27]. Some studies, however, found either no change [33] or increases [34] in blood flow from waking to NREM sleep. After controlling for the global changes in brain function across states, several regional variations have been observed during NREM sleep. Blood flow has been shown to negatively correlate with the presence of NREM sleep in the anterior cingulate [35, 36, 37], the pontine reticular formation [35, 37], the thalamus [33, 35, 36, 37], the basal forebrain/hypothalamus [38], the amygdala [38], the orbitofrontal cortex [35, 38], and in the heteromodal association cortex [33, 36, 38]. These changes are consistent with preclinical studies showing reductions in brainstem, basal forebrain, and hypothalamus sources of ascending activation. Declining function in the amygdala raises the possibility that this structure modulates activity in ascending activating structures. Increased baseline activity in any of these structures in the elderly, therefore, may shift cortical function towards the more activated sleep/wake periods of waking and REM sleep.

Age-related morphological changes in the brain

As noted in the functional neuroimaging studies of sleep above, various forebrain structures play important roles in the generation and manifestation studies of sleep. In this light, it is significant that there is an extensive literature of the effects of aging on both gross and regional brain morphology, though studies demonstrating the relationships between these brain changes and sleep have not been well characterized. Regionally, these changes are most pronounced in the lateral pre-frontal cortex, a region implicated in the homeostatic properties of sleep due to the high regional density of slow wave sleep production in this area. These changes seem to result from lower synaptic densities in late-life adults. Parallel changes in neurotransmitter systems that are important for pre-frontal cortex function include age-related reductions in dopamine concentration, transporter availability, dopamine D2 receptor density, and serotonin receptor (5-HT2) availability. Parallel life-long declines in neurocognitive function include those related to pre-frontal cortex function such as cognitive information processing speed, working memory, and encoding of information into episodic memory. While changes in brain metabolism across the lifespan have been noted, many of these changes appear secondary to the age-related changes in brain morphology, since after correction for the problem of partial volume averaging of PET signals due to brain atrophy, age-related changes in brain metabolism or blood flow are not found.

Candidate brain structures that may function abnormally during sleep in the aged

Available evidence therefore, points to several brain structures in a distributed system that is responsible for the generation, maintenance, and modulation of behavioral state control.

Declines in slow wave sleep in the elderly may be accounted for by several brain mechanisms. First,

there may be age-related changes in the structure or function of the ventrolateral pre-optic nucleus and/or pre-frontal and frontal cortex that are known to be important in the production of sleep, especially of slow wave sleep. Second, there may be an abnormally increased function in brain systems mediating arousal that prevents the spontaneous occurrence of slow wave sleep. The structures that make up this distributed system include the pontine reticular formation, the basal forebrain, the hypothalamus, the thalamus, and the amygdala.

Alterations in sleep continuity can also be theorized to result from the same mechanisms that account for the slow wave sleep changes associated with aging. Factors that prevent the occurrence of deeper NREM sleep in the elderly would also be expected to lead to lighter, more fragmented sleep, thereby increasing sleep continuity disturbances.

Changes in REM sleep in the elderly may be related to the brain structures that either generate or maintain REM sleep. These structures include the pontine reticular formation, the basal forebrain and hypothalamus, the amygdala, and anterior paralimbic structures such as the anterior cingulate cortex and the medial pre-frontal cortex.

Effects of age on NREM sleep-related functional neuroanatomy across young adulthood

We explored age-related effects in young adult and mid-life healthy subjects studied to date. Two groups were formed, a young adult group (N = 7, 5 females and 2 males, mean + s.d. age = 25 ± 2.8 years) and a mid-life group (N = 7, 5 females and 2 males, mean ± s.d. age = 43 ± 3.8 years). EEG sleep measures were compared from a baseline night of sleep. At these sample sizes, the only significant difference was in an automated measure of delta sleep (mid-life subjects < young adults, mean ± s.d. counts for mid-life subjects = 6154 ± 2520; for young adults = 9403 ± 2371; $t = -2.5$, $df = 12$, $p = 0.03$).

Our initial analysis was a study of the effects of age on relative metabolism while awake. Young subjects had increased relative metabolism in broad regions of largely frontal heteromodal association cortex with some increases in smaller areas of parietotemporal cortex. Across all subjects we explored the effects of age on relative cerebral metabolism during NREM sleep. Increasing age was associated with decreases in relative metabolism in broad regions of association cortex, including frontoparietal areas. Relative metabolism in the thalamus also declined with advancing age. In contrast, relatively fewer areas showed increases in relative metabolism during NREM sleep with advancing age. Areas that did included more inferior regions of cortex such as the inferior temporal lobes, orbitofrontal cortex, and occipital/parahippocampal regions. In a second analysis, we studied changes in regional brain function from waking to NREM sleep in the young and mid-life adult groups. The young subjects showed greater decreases from waking to NREM sleep in relative metabolism in the anterior cingulate cortex, the insular cortex, and scattered frontal and pre-frontal cortex. The mid-life subjects showed greater decreases in the cerebellum and in diffuse regions of parietotemporal heteromodal association cortex.

In a third analysis, we correlated NREM slow wave sleep by waking metabolism. Given that slow wave sleep declines begin in the third to fifth decades, this may provide early insights into the aging process that are reflected by a loss of slow wave sleep. We demonstrated that the declines in slow wave sleep across young adult aging are associated with declines in relative glucose metabolism in the pre-frontal and related dorsal paralimbic mesocortex. Relative metabolism in structures that promote behavioral arousal were negatively associated with the production of slow wave sleep, yet these changes were not appreciably affected by age.

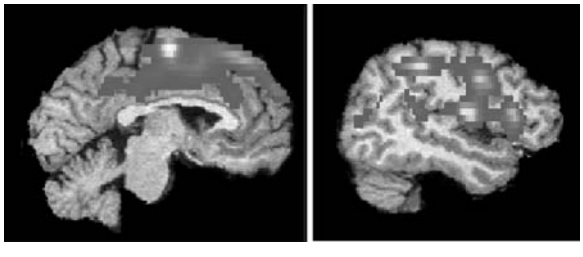


Figure 41.2. Metabolism correlates more positively with slow wave sleep than with age over the third to fifth decades of life. See plate section for color version.

Effects of age on REM sleep-related functional neuroanatomy across young adulthood

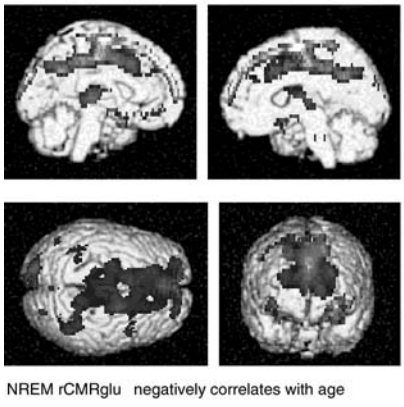
Six healthy subjects ranging in age from the 20s to 40s received assessments of relative cerebral glucose metabolism during REM sleep in our laboratory. Across all subjects we explored the effects of age on relative cerebral metabolism during REM sleep. Increasing age was associated with decreases in relative metabolism in bilateral regions of frontal and parietal cortex, the anterior and dorsomedial regions of the thalamus, and the posterior cingulate cortex. In contrast, with advancing age only the more inferiorly located primary limbic structures, including the bilateral amygdalas, the periamygdalar cortex, the ventral striatum and the hippocampus, showed increases in relative metabolism during REM sleep. These studies suggest that even during REM sleep there are widespread reductions in association cortex function with advancing age. Further, the "limbic thalamus," which connects with the medial pre-frontal cortex and anterior cingulate cortex, areas that are traditionally more active during REM sleep, was less active with advancing age. Given the role of these regions in motivated behavior and adaptive cognitive functions, the decreased activation of this region with advancing age may reflect age-related declines in adaptive behavior.

Functional neuroimaging studies in older subjects

Several brain morphological studies have relevance to models of the functional neuroanatomy of sleep in aging [39, 40]. In one study, two MR-based approaches to partial-volume correction of PET images were compared using simulations and a multi-compartment phantom. A two-compartment (brain, CSF) method corrects PET data for the diluting effects of cerebrospinal fluid spaces. A three-compartment (gray/white matter brain, CSF) method also accounts for partial-volume averaging between gray and white matter. The three-compartment method was highly accurate in gray matter recovery, although it was suspect to all errors tested, including image segmentation and PET-MR registration. These studies show that underestimation of cortical activity associated with partial-volume averaging of gray matter with surrounding CSF spaces is particularly problematic in conditions in which there may be an alteration in cortical tissue, such as in late-life subjects. A second study showed that age-related cerebral atrophy accounts for much of the variance in studies of age-related declines in cerebral blood flow. Twenty-seven healthy subjects (age range 19–76) received cerebral blood flow PET studies. An MR-based atrophy correction algorithm was applied to the PET data. Tissue correction factors were significantly smaller in the elderly in all regions examined (smaller factors = greater proportion of CSF). While a significant reduction in blood flow was observed in aged subjects, this effect was removed after the correction for atrophy was applied. These studies show that aging is associated with significant cerebral atrophy. Given the role of the cortex in the generation of slow wave sleep, this age-related atrophy may be related to the abnormal slow wave sleep generation seen in older subjects. If so, this provides evidence for a *functional* deterioration that is attributable to the *anatomical* cortical changes associated with aging.

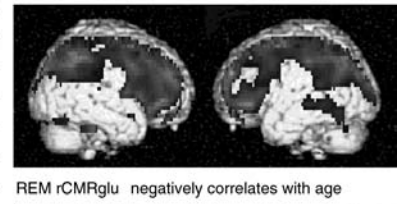
We completed a preliminary analysis of PET studies of REM and NREM sleep in two late-life subjects (Figure 41.3). We then included the data with that from studies in 14 mid-life subjects in an analysis exploring the effects of age on relative cerebral metabolism. In NREM sleep, age negatively correlated with a broad region of pre-frontal and anterior cingulate cortex. During REM sleep, age negatively correlated with a broad extent of heteromodal pre-frontal and parietal association cortex and positively with a large collection of brainstem, limbic, and paralimbic cortex. This pattern of changes has been replicated in a larger sample of aging subjects.

A separate study tested the hypothesis that sleep loss in late-life is related to either brain atrophy and/or an inability to reduce pre-frontal metabolism during sleep. We assessed brain size, metabolism, and sleep in young to mid-life (mean age + s.d. = 31.5 + 8.1 years, N = 15) and late-life (N = 15, mean age + s.d. = 78.6 + 4.6 years) healthy subjects. Magnetic resonance imaging studies defined brain volumes, [18F] FDG positron emission tomography (PET) scans during waking and sleep defined cerebral glucose metabolism [41], and EEG sleep studies defined sleep stages. We used the automated labeling pathway (ALP) method to assess brain volumes [42]. We focused on whole brain and bilateral mid-frontal gyrus (lateral pre-frontal cortex) regions given reports of age-related atrophy in these regions. PET measures included both absolute and relative measures of metabolism in the identical

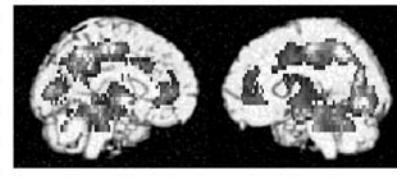


NREM rCMRglu negatively correlates with age

Gender	Male	Male
Age (years)	89	73
Sleep latency (min)	14	9
Time spent asleep (min)	321	425
Sleep efficiency (%)	74	89
Stage 1 (%)	12	9
2 (%)	66	74
3 (%)	1	0
4 (%)	0	0
REM (%)	21	17
REM latency (min)	18	77
Delta EEG spectral power	24	5
Beta EEG spectral power	0.06	0.06



REM rCMRglu negatively correlates with age



REM rCMRglu positively correlates with age

Figure 41.3. A preliminary analysis of PET studies of REM and NREM sleep in two late-life and 14 mid-life subjects. In NREM sleep, age negatively correlated with a broad region of pre-frontal and anterior cingulate cortex (left panels). During REM sleep, age negatively correlated with a broad extent of heteromodal pre-frontal and parietal association cortex and positively with a large collection of brainstem, limbic, and paralimbic cortex (right panels). See plate section for color version.

regions defined by the ALP method. All PET measures were atrophy-corrected to minimize partial volume averaging. We performed a factor analysis of brain anatomical and metabolic measures to reduce the number of variables. Next, we used univariate regressions to independently describe the relationship of age across all subjects to these brain factors and to sleep. We then performed multiple regressions to determine the best predictors of total sleep time, REM sleep time, and EEG delta spectral power, using as potential predictors age group (young to mid-life vs. late-life adults), the brain factors that showed univariate relationships with sleep, and age group by brain factor interactions.

The factor analysis and univariate regressions yielded two brain factors that were associated with sleep. Relative metabolism in the mid-frontal gyrus during sleep (frontal sleep metabolism) had the highest loading on one factor and mid-frontal gyrus volume had the highest loading on the second factor. Total sleep time, delta spectral power, and REM time as well as the mid-frontal gyrus volume factor all showed reductions with increasing age (Pearson's r, p-values = −0.71, <0.0001; −0.56, <0.002; −0.70, <0.0001; −0.75, <0.0001, respectively). The brain factor frontal sleep metabolism increased with increasing age (Pearson's r, p-value = 0.51, 0.004). The multiple regressions demonstrated that age, frontal sleep metabolism, and mid-frontal gyrus volume that included age group by brain factor interactions, were those that best predicted the sleep measures total sleep time, delta sleep power, and REM time. The best fit models (based on the AIC criterion) showed there was a significant interaction between age and the mid-frontal gyrus factor (parameter estimate [standard error] = 44.9 (20.9), p = 0.0415) for total sleep time and significant age by frontal sleep metabolism interactions for delta spectral power and REM time (0.72 [0.33], p = 0.0376 and 1.37 [0.53], p = 0.0158, respectively).

This study was the first to assess the relationships between age-related changes in brain size and sleep metabolism, and age-related changes in sleep using multimodal anatomical and functional neuroimaging and polysomnographic assessments. By focusing on "local" factors at the level of the cortex [41, 43, 44, 45] these results are the first to emphasize that the neural substrates of age-related changes in sleep are related to well-known changes in the brain across adulthood, especially in regions shown to play a role in the restorative properties of sleep [46]. These results show that age-related changes in the lateral pre-frontal cortex, anatomically and metabolically, account for roughly 50–60% of the age-related reductions in sleep. The relationship between mid-frontal gyrus volume loss and sleep loss was significant not only for total sleep, but for REM sleep as well. REM sleep is generated by the brainstem and preferentially activates limbic and paralimbic cortex [47]. The current findings emphasize an important role for higher order association cortex in maintaining REM sleep.

An increase in relative metabolism during sleep in the mid-frontal gyrus was also associated with sleep loss. Metabolism in this region normally declines from waking to sleep [41]. Higher metabolic activity during sleep may reflect the aging brain's lost ability to descend into deep sleep. Alternatively, increased metabolic activity during sleep may reflect a persistence of

activation from the brainstem or hypothalamus [48]. The finding that the brain substrate of sleep, i.e. the cortex, has atrophied across adulthood strengthens the argument that the ability to descend into a deeper sleep has been lost.

The shift in focus of the loci of age-related sleep alterations to the cortex, as suggested by the current findings, suggests that there are physiological limits to the ability to sleep in old age related in part to declining brain tissue. Acknowledgment of these limitations by caretakers may avoid unrealistic expectations for sleep in elderly persons that might lead to psychological distress and excessive pharmacological sedation. Experimental trials to enhance sleep in late-life should include neuroprotective or neurotrophic interventions as well as interventions that reduce metabolic activity in the lateral pre-frontal cortex during sleep.

The current study focused on large regions of the brain, in part related to the limited spatial resolution of PET, thereby limiting interpretations regarding the role of small nuclei in the brain in age-related declines in sleep. Still, the present study suggests that between 50% and 60% of the variance in age-related sleep loss is related to age-related changes in brain size and metabolism, especially in the lateral pre-frontal cortex.

Summary: a functional neuroanatomical model of the effects of aging on sleep

In the context of preclinical studies and the brain imaging data, we have developed the following model of the functional neuroanatomy of sleep in the elderly (Figure 41.4). First, there are well-defined shifts in forebrain function across the states of waking and NREM and REM sleep. In waking, cortical function is active in primary and association cortex, driven by ascending monoaminergic brainstem input. In NREM sleep, there is a pronounced deactivation of thalamocortical pathways in the absence of ascending activation. In REM sleep, there is intrinsic activation of cortex by ascending cholinergic brainstem input, but with regionally specific activation of limbic and paralimbic cortex. EEG sleep studies support NREM and REM sleep changes in aging that predict health outcome. Alterations in sleep continuity and slow wave sleep may represent structural and functional declines in thalamo-cortical function associated with aging, most specifically in pre-frontal and parietal association cortex as well as in dorsal paralimbic mesocortex. Additionally, brain structures known to be involved in promoting behavioral arousal, such as the

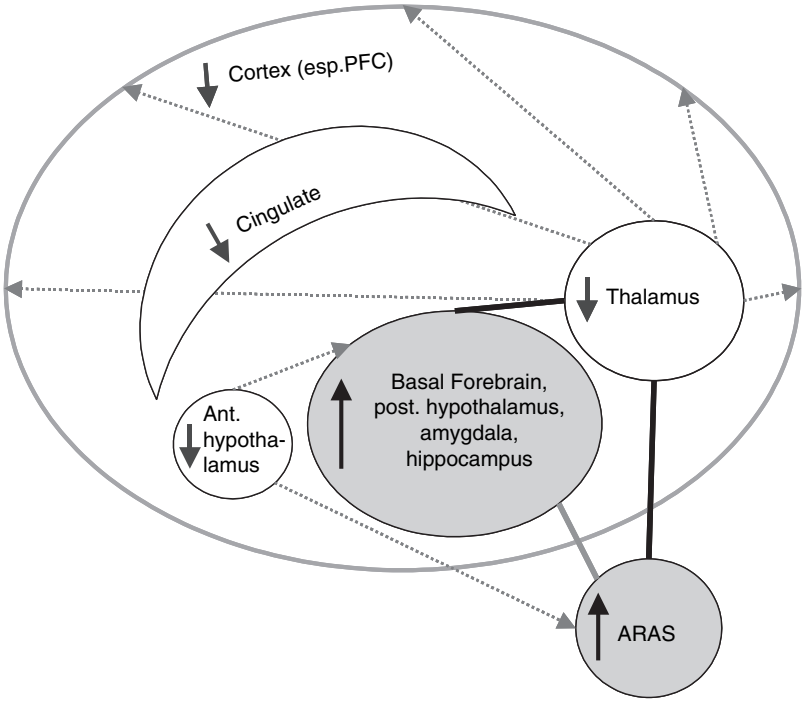


Figure 41.4. A functional neuroanatomical model of the effects of aging on sleep. See text for description of relationships.

ascending reticular activating system, the basal forebrain/posterior hypothalamus, amygdala, and hippocampus, may have increased relative function in the elderly that inhibits slow wave sleep production. Alterations in REM sleep may reflect both a loss of generalized heteromodal cortex structure and function, as well as a shift towards primary limbic (e.g. amygdala) activation of forebrain structures.

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