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EDITED BY

Barry S. Oken, MD

# Complementary Therapies in Neurology

## AN EVIDENCE-BASED APPROACH

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EDITED BY

Barry S.Oken, MD

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**The Parthenon Publishing Group**
International Publishers in Medicine, Science & Technology
A CRC PRESS COMPANY
BOCA RATON LONDON NEW YORK WASHINGTON, D.C.

Published in the USA by The Parthenon Publishing Group 345 Park Avenue South, 10th floor New York NY 10010 USA
This edition published in the Taylor & Francis e-Library, 2005.



Published in the UK and Europe by The Parthenon Publishing Group 23–25 Blades Court Deodar Road London SW15 2NU UK

**Library of Congress Cataloging-in-Publication Data** Complementary therapies in neurology: an evidence-based approach/edited by Barry S.Oken p. ; cm Includes bibliographical references and index. ISBN 1-84214-200-3 (alk. paper) 1. Nervous system—Diseases—Alternative treatment. I. Oken, Barry S. [DNLM: 1. Complemenatry Therapies. 2. Nervous system Diseases—therapy. 3. Evidence-Based Medicine. WL 140 C737 2003] RC350.A45C66 2003 616.8′046–dc22 2003055844

**British Library Cataloguing in Publication Data** Complementary therapies in neurology: an evidence-based approach 1. Nervous system—Diseases—Alternative treatment I. Oken, Barry S. 616.8'06

ISBN 0-203-49457-1 Master e-book ISBN

ISBN 0-203-59639-0 (Adobe e-Reader Format)
ISBN 1-84214-200-3 (Print Edition)

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# Preface

There is a significant use of complementary and alternative therapies throughout the world. Many of these therapies may offer benefits to people with neurological diseases. Some of these benefits are proven, some are not well studied, and some of these purported benefits have already been shown to be lacking. These complementary therapies may interact with conventional treatments, so it is critical for conventionally trained health-care providers to be knowledgeable about the complementary therapies their patients are using. Despite these facts, there is a lack of knowledge of complementary therapies by many conventionally trained physicians. For all these reasons, it seemed an appropriate time to provide a book focusing on complementary therapies for neurological disorders. This book is targeted to any health-care provider who sees people with neurological diseases. While there are other books in the general area and even one for neurological disorders, the scientific level of all the chapters, especially those sections organized by disease states or conditions, should be accessible to even the most scientifically stringent, conventionally trained physicians, including neurologists.

The book is organized into two main sections following the introductory chapter. The first section discusses many of the complementary and alternative therapy modalities. The second section is structured similarly to conventional neurology textbooks; it is organized by disease states or conditions and reviews relevant evidence in a very conventional manner.

The choice of topics for the first portion of this book was based in part on the amount of evidence available and on the amount of use. Some therapies were not chosen, because there was too little published clinical data regarding neurological disorders. These therapies may have well-established and wide medical use but not in neurology to any degree, or they may be used for neurological disorders but without much evidence.

Music, dance and art therapy could all be considered aspects of mind-body medicine. These therapies are well-established complementary therapies with formal educational programs at the undergraduate or graduate level, national organizations (www.arttherapy.org, www.adta.org and www.musictherapy.org) and accreditation processes. While there are randomized controlled trials of these therapies for some indications, the evidence for most neurological disorders is limited. There are other complementary therapies such as use of magnetic fields and aromatherapy that have no specific chapter focused on these treatments, but relevant data are discussed in the disease-oriented chapters. There are several modalities that are usually considered more within the realm of conventional medicine and are not discussed in any detail; these include transcranial magnetic stimulation and hyperbaric oxygen. There are groups of complementary therapies, such as energy-based therapies, for which data are limited and these also are not discussed in any detail (e.g. Reiki, therapeutic touch, Qigong). Homeopathy is discussed only briefly in the chapters on epilepsy and naturopathy.

Some of the chapters include historical perspectives; these are particularly the chapters on traditional Chinese medicine and ayurveda. The utility of modalities such as acupuncture does not depend on acceptance of the historical perspectives, and some even feel that this historical perspective may be impeding its scientific development. However, it is of some importance to know these historical perspectives and to refine the explanatory concepts with empirically testable theories on the mechanisms of action.

The goal for this book is to be a useful resource to conventional or complementary health-care providers who are trying to optimize the health of their patients.

# Acknowledgements

I would like to acknowledge all the clinical researchers whose published clinical trials and insights have produced the knowledge upon which this book is based, and all the government and non-government organizations that have funded the research discussed in this book. The US National Institutes of Health National Center for Complementary and Alternative Medicine has supported the Oregon Center for Complementary and Alternative Medicine in Neurological Disorders (ORCCAMIND) (www.ohsu.edu/orccamind) which has been under my direction since 1999. I have appreciated the discussions I have had with all the researchers at ORCCAMIND concerning many of the topics discussed in this book.

I would like to thank all the members of my research staff who have been excellent at carrying out many research projects and allowing me to focus some time on this book. I would like specifically to acknowledge Andy Fish for organizing the chapters and correspondence from both the authors and CRC Press, and Shirley Kishiyama who helped with editing and graphics.

# DEDICATION

To my family, for their love and support

# Color plates

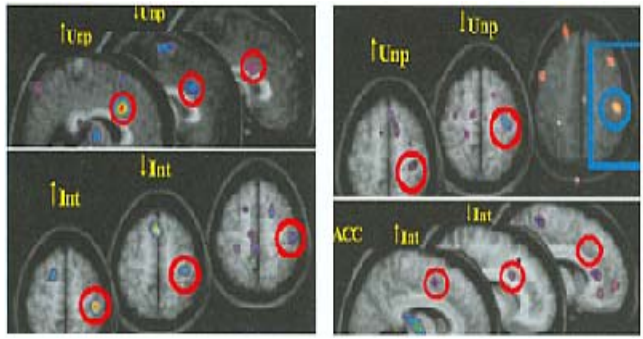


**Plate 1** Regional cerebral blood flow changes in pain-related activity within primary somatosensory cortex (S1) and anterior cingulate cortex (ACC) associated with hypnotic suggestions for increased pain (↑), decreased pain (↓) and increased minus decreased-pain (↑–↓) intensity (Int), and unpleasantness (Unp) during the sensory-modulation experiment (from reference 54) and the affective-modulation experiment (from reference 53). Modulatory effects of suggestions for ↑ and ↓ pain (Int or Unp) are revealed by subtracting positron emission tomography (PET) data recorded during the warm hypnosis-control condition from the ↑ pain (Int or Unp) and the ↓ pain (Int or Unp) conditions and the ↑–↓ pain (Int or Unp) involved subtracting ↓ pain (Int or Unp) condition from the ↑ pain (Int or Unp) condition. Horizontal and sagittal slices through S1 and ACC, respectively, are centered at the

activation peaks observed during the relevant suggestion condition. Copyright 2001 by the American Physiological Society. Reproduced with permission

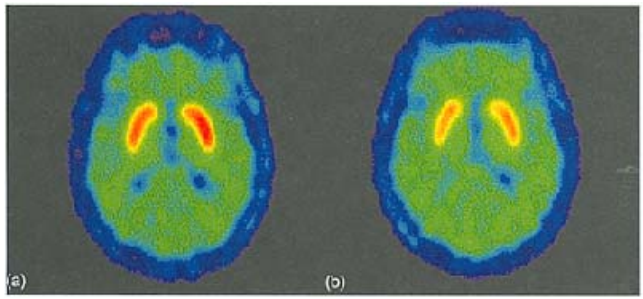


**Plate 2** [$^{11}$C]Raclopride-positron emission tomography scans of a patient with Parkinson's disease at baseline (a) and after administration of placebo (b) during a double-blind experiment where the subjects received placebo or a dopaminergic agent (apomorphine) at different times. The diminished striatal radioactivity observed following placebo is thought to reflect an increase in synaptic dopamine in this type of scan. Copyright 2002 Elsevier Science Ltd. Reproduced with permission from de la Fuente-Fernandez R, Stoessl AJ. The placebo effect in Parkinson's disease. *Trends Neurosci* 2002; 25:302–6

# 1
# Complementary and alternative medicine; overview and definitions

*Barry S.Oken*

*Complementary Therapies in Neurology: An Evidence-Based Approach*
Edited by Barry S.Oken
ISBN 1-84214-200-3 

A number of terms have been used to describe a group of clinical activities that have traditionally been outside the scope of conventional or allopathic medical practice. The most common term is *complementary and alternative medicine* (CAM) and this abbreviation will be used throughout this book despite its potential shortcomings. CAM is not an ideal term, in part because the therapies are usually not alternative to conventional medicine as practiced by most of the population but are complementary, with the two approaches used at the same time. The CAM grouping is somewhat artificial, as there is no inherent link between all aspects of what is considered CAM: unconventional uses of magnets do not have much in common with dance therapy or high-dose vitamin therapy. There have been some formal attempts to define the therapies that are considered CAM. The initial definition of CAM was simply clinical practices not taught at most medical schools and not generally available at most hospitals. Given that most medical students are now taught about some dietary supplements and many medical students are at least exposed to therapies such as acupuncture this is no longer a useful definition. In an editorial in *The New England Journal of Medicine,* Angell and Kassirer suggested that there is no such thing as alternative medicine. 'There is only medicine that has been adequately tested and medicine that has not, medicine that works and medicine that may or may not work'[1]. While the practice of evidence-based medicine is an excellent goal, there are always gaps in the knowledge base. Clinicians frequently have to make clinical decisions in the absence of clear evidence. Pediatricians may have to make decisions about use of drugs based on clinical trial data from adults, and geriatricians may have to make similar decisions for their centenarians based on clinical trial data with essentially no centenarians, even for Alzheimer's disease. Clinical trials often exclude patients with multiple medical problems that may confound the focused objective of determining the efficacy of a treatment for a specific condition. Given these concerns, the above-noted editorial regarding the terminology is simplistic.

*Integrative medicine* is another term that is used to describe this group of therapies and represents an attempt to merge CAM with conventional medicine. Fellowships in integrative medicine are now offered at conventional medical institutions. Some feel that the term 'integrative medicine' is not simply adding CAM to conventional medicine but

should be used to describe a system of care where 'wellness and healing of the entire person (biopsycho-socio-spiritual dimensions)' is the primary goal[2].

Whatever the terminology, it is reasonable to group together certain therapies that have historically been outside conventional medical practice. The US National Institutes of Health (NIH) set up the National Center for Complementary and Alternative Medicine (NCCAM, http://www.nccam.nih.gov/) to study those practices that have varying degrees of evidence to support their use. NCCAM uses the following classification system of CAM practices, with examples of each:

(1) *Alternative medical systems*—oriental medicine, naturopathy, homeopathy, ayurveda;
(2) *Mind-body interventions*—meditation, hypnosis, yoga, tai-chi, dance, music and art therapy;
(3) *Biologically based therapies*—botanicals, orthomoleculars and other dietary supplements;
(4) *Manipulative and body-based systems*—chiropractic, osteopathic, massage therapy;
(5) *Energy therapies*—

   (a) biofield therapies (use of energy that purportedly surrounds and penetrates the human body), e.g. Reiki, Qi gong, therapeutic touch
   (b) bioelectromagnetic-based therapies—unconventional uses of electromagnetic fields.

It should be noted that the inclusion of orthomoleculars and other dietary supplements in this list causes it to include practices that are completely adopted by conventional medicine, in terms of both research and clinical use, e.g. the case of coenzyme Q10 in Parkinson's disease.

The use of CAM practices is considered conventional in many parts of the world, including Europe, where German medical physicians have routinely prescribed botanicals for decades. In the USA the growth of CAM has been most prominent over the past decade, in large part related to increased interest from the public but also to the 1994 US Dietary Supplements Health and Education Act (DSHEA). The US DSHEA freed manufacturers of dietary supplements (including vitamins, minerals, botanicals and hormones) from much regulatory oversight, although some still remains. This resulted in the marketing of greater numbers of dietary supplements directly to the public.

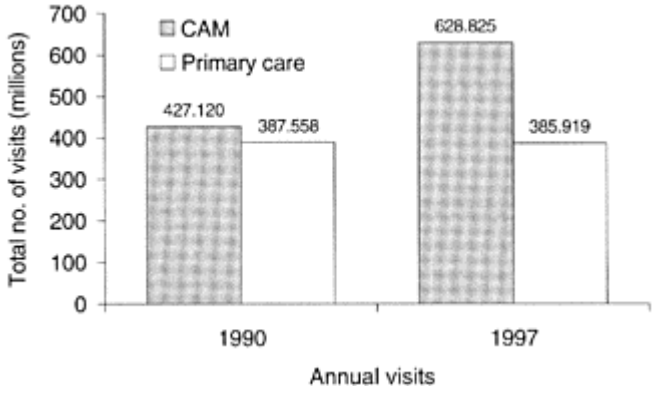


**Figure 1** Trends in annual visits (1990 and 1997) to practitioners of complementary therapies (CAM) compared to visits to primary care physicians in the USA. Reproduced with permission from reference 3

Many aspects of CAM use in the USA have been studied by Eisenberg and colleagues using national surveys. The growth during the 1990s is shown in Figure 1[3]. The use of at least one of 16 CAM therapies during the year prior to a telephone interview increased from 33.8% in 1990 to 42.1% in 1997. Relaxation therapies, botanicals, massage and chiropractic were the most common therapies used. The amount of money spent for complementary therapies in the USA was estimated to be $30 billion (US) in 1997 (Figure 2).

The users of CAM are varied. Since CAM use has been increasing over time, CAM use is greater among those born in 1965–79 than those born before 1945[4]. CAM is often used for health promotion or disease prevention rather than for a specific disease, with over half the CAM therapies in the US survey having been used at least in part to 'prevent future illness from occurring or to maintain health and vitality'[3]. CAM use is greater for common

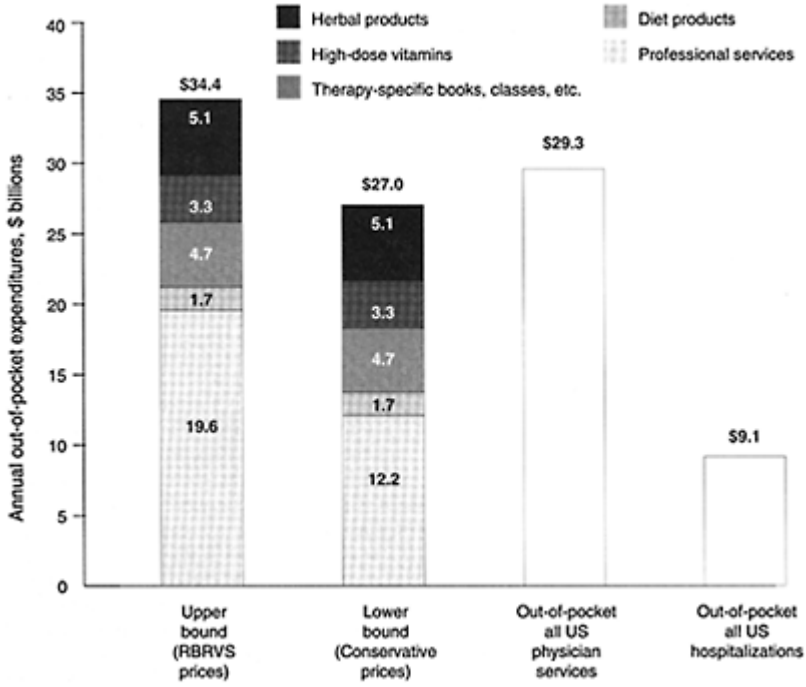


**Figure 2** Estimated annual out-of-pocket expenditures for complementary therapies compared to conventional medical services in the USA. Reproduced with permission from reference 3

chronic disorders for which conventional treatment options are limited, such as back pain and anxiety, as well as for life-threatening conditions for which no cures are currently available. There is a correlation between educational level and CAM use, with higher CAM use associated with more years of education[5]. There is also higher use among certain ethnic groups where CAM use is considered more traditional. Almost all (96%) CAM users also see conventional medical doctors[3,5].

The reasons given for use of CAM therapy are varied. In one study, the most common reason given for CAM use was its effectiveness[5]. In one US public survey in which the respondents used both conventional and CAM therapies, the respondents thought the CAM therapy was better for back and neck conditions and conventional medicine was better for management of high blood pressure[6]. While both approaches may have something to offer patients with each of these conditions, the public appears to have some insight into the utility of these various therapies for various conditions. The use of CAM was similar for people who were satisfied and those who were dissatisfied with

conventional medicine practitioners, and people overall had similar degrees of confidence in their CAM and non-CAM practitioner[6].

Many complementary therapies do not have the same degree of clinical trial evidence that many conventional therapies have. This led to the statement mentioned above that there is no such thing as alternative therapy, just therapies that have been proved useful and therapies that may or may not be useful[1]. However, by strict evidence-based medicine criteria there is usually no specific evidence for most of what any clinician does in day-to-day practice, ranging from treating patients with common but highly variable syndromes, such as respiratory infections and low back pain, to diseases where therapies have been shown to be useful but only in a subset of patients. The lack of evidence for most CAM therapies presents a significant problem when trying to determine their utility. It is an even larger problem because the effect of these therapies is often less than that for conventional therapies. As a result, fairly large trials would be needed to document these effects and it is unclear whether this extra cost is always worthwhile. Research will help answer some questions but limited resources force prioritization of the research agenda[7] and many questions will not be imminently answered.

There is often a significant difference in perspectives between some practitioners of conventional medicine and CAM practitioners. The perception by some in the CAM community that the scientific methodology was not advanced enough to allow for quality studies in CAM necessitated publication of conclusions from an NIH working group. 'Contrary to the assertions of many researchers and alternative medicine practitioners, established methodologies…and data-analytic procedures are quite satisfactory for addressing the majority of study questions related to alternative medicine…'[8]. More study design development would be helpful for issues related to some necessarily non-blinded interventions (e.g. yoga), individualization of therapy, and better outcome measures related to quality of life and wellness. However, currently available techniques are sufficient for much of the needed research. While some CAM practitioners may minimize the usefulness of scientific methods, some conventional medical practitioners may minimize the utility of CAM independently of already published data, highlighting its usefulness for at least some conditions[9]. Many practicing conventional physicians judge complementary therapies to be moderately useful and make referrals to complementary providers[10,11], but this perception is not universal. The bias against unconventional therapies stemming in part from the lack of experimental evidence was experimentally demonstrated in a study of medical experts reviewing a manuscript for a 'peer-reviewed publication'. Two essentially identical versions of a short research paper were produced, the difference being that one was using a potentially orthodox treatment of obesity (hydroxycitrate) and the other was unconventional (homeopathic sulfur). The only difference in the papers besides the name of the drug was the several lines in the beginning of the paper that cited different references for justification. One version or the other was randomly sent to many conventionally trained reviewers with 141 evaluable responses. There was a significant reviewer preference for the conventional treatment paper despite identical methodology and outcome data[12].

The use of vitamin E presents some of the issues unique to CAM. In 1999, the American Heart Association issued a statement that the published evidence did not generate enough data for vitamin E supplements to be a population-wide recommendation[13]. At approximately the same time, it was estimated that about 50% of

American cardiologists were taking vitamin E supplements[14]. American cardiologists were using different and less cautious decision-making criteria for their own health compared to what they were recommending to the population. This situation is not so different from much of CAM where reasonably safe, often low-cost interventions may have suggestive evidence as to their utility but not the same weight of evidence that would be required for US Food and Drug Administration (FDA) approval of a standard pharmaceutical agent for a particular disease. Treatments with essentially no risk, available to people without a prescription and generally paid for out-of-pocket, are often used before there is the same level of evidence required for drugs, often with higher risk, that have gone through formal assessment processes required by the FDA regulations or third-party payers. While this book tries to

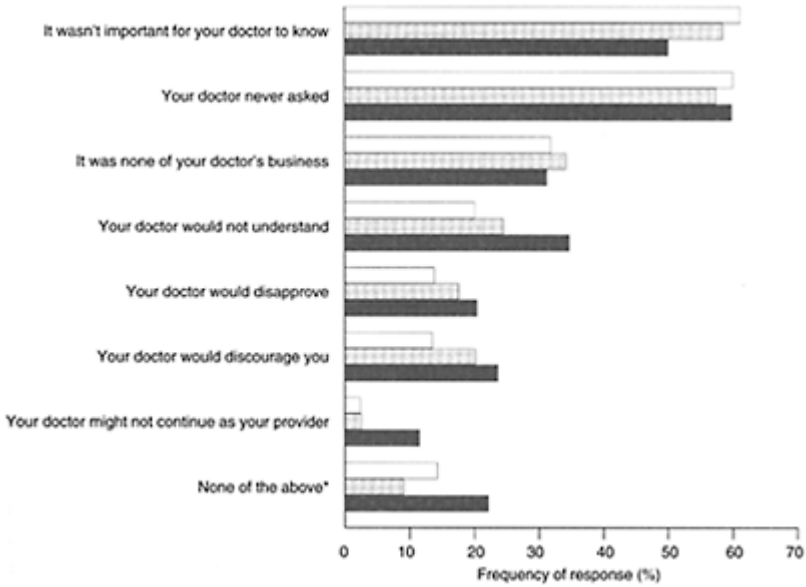


**Figure 3** Reasons for non-disclosure of complementary and alternative medicine (CAM) use in a group of 726 out of 2055 total respondents in a US telephone survey who both used a complementary therapy and saw a medical doctor during the past year. Reasons for non-disclosure of: any therapy included in the survey (*n*=726); therapies with a recognized potential risk for adverse events—namely herbal remedies, chiropractic,

naturopathy, megavitamins, and chelation therapy (*n*=188); ■ therapies among respondents who reported having relatively 'severe' medical condition—cancer, coronary artery disease, or diabetes mellitus—in the past 12 months (*n*=33). Respondents said 'yes' or 'no' to each of the possible reasons. Overall, about two-thirds of subjects did not disclose at least one CAM therapy to their conventional medical doctor. *This response choice was not read but was volunteered by respondents. Reproduced with permission from reference 6

focus on evidence-based therapies, it should be clearly stated that evidence basis without attention to risk-benefit and cost-benefit issues is not the whole story, as shown by the American cardiologists and vitamin E.

One important issue is for both conventional and complementary medicine practitioners to discuss all medical interventions with their patients. Conventional medical health-care providers' lack of knowledge of the complementary therapies their patients are using and a similar lack of knowledge by CAM practitioners of the conventional therapies may have a significant negative impact on medical care, e.g. drug-botanical interactions. Half or more of patients do not disclose their complementary therapy use to their convention physician[6,15,16], even when specifically asked on a written questionnaire[16]. This lack of communication between patients and their conventional physicians is present even when the patient has a life-threatening illness such as cancer and when the therapies clearly may interact with conventional treatments, such as botanicals. Some of the reasons for non-disclosure are shown in Figure 3.

As conventional medical practitioners try to utilize complementary medicine techniques for their patients, it becomes clear that the certification and regulation is not standard as is that for conventional medicine. This information is discussed in more detail in the relevant chapters. Osteopaths have had similar licensure to those holding MD degrees for many years. Chiropractors are also licensed by state boards in all 50 states and the District of Columbia. Statutory licensure is less common for other non-conventional medical professions: 41 states license for acupuncture, 31 for massage therapy and 11 for naturopathy[17]. Owing to the regulation issues as well as other reasons, problems arise when conventionally trained clinicians recommend these therapies. Issues related to advising patients who seek CAM therapy and ethical considerations for CAM therapies in conventional medical settings have been published[18,19], but it is incumbent on the conventional practitioner to have a reasonable degree of CAM knowledge.

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# SECTION I:
# THE THERAPIES

# 2
# Botanicals—quality, efficacy, safety and drug interactions

*Amala Soumyanath (née Raman)*

*Complementary Therapies in Neurology: An Evidence-Based Approach*
Edited by Barry S.Oken
ISBN 1-84214-200-3 

The use of botanical health products (herbal products), sold as dietary supplements, is becoming a common phenomenon in Western society. In a 2002 study[1], total sales of dietary supplements in the USA were estimated at US$17 billion and annual sales in the nutritional market are estimated to grow in the 6% range for the next few years, although the increase in the herbal products category may be more modest. Retail channels accounted for 85% of sales, suggesting that the intervention of a complementary or alternative medicine (CAM) practitioner is uncommon in the use of botanical products by consumers.

A survey by Eisenberg and colleagues[2] in 1998 found that the percentage of adults in the USA who had used a botanical product during the preceding year increased from 2.5 to 12.1% between 1990 and 1997. Only 15% of these had consulted a CAM practitioner. The most common means of acquiring these products was by self-selection from commercial outlets. About 19% of patients taking prescription medicines were concurrently using herbal products or megavitamins, but only 40% of patients taking these alternative therapies disclosed this fact to their physician.

The continued and increasing use of botanical products, often alongside conventional treatments, and without the involvement or knowledge of a health-care professional, requires us to examine their potential efficacy in treating disease, and the likely risks, i.e. lack of efficacy or poor safety including potential interactions with conventional drugs. This article examines the unique nature of botanical products, quality control issues, their potential use in conditions involving the nervous system and the factors that may compromise or promote their safety and efficacy.

## WHAT ARE BOTANICAL PRODUCTS?

Botanical products are derived from plant sources and may be presented in a number of different forms.

*Whole herbs* (‘crude drugs’), usually dried, generally consist of the particular part of the plant associated with medicinal effects, e.g. calendula flowers, liquorice root, peppermint leaves. They may be obtained *via* a CAM practitioner, or bought in shops

selling botanical products. The herbal material is infused in hot water by the consumer to make an herbal 'tea'. Thus, the components ingested would be hotwater-soluble ones only.

*Powdered herbs* are also available commercially. They may be packaged either in loose powder form or in tea-bags for making infusions, or may be put into conventional dosage forms such as capsules or tablets. In the latter situation, all the constituents of the herb would be ingested.

*Extracts of herbs* can be made using various solvents. These range from simple tinctures made with aqueous ethanol, to more complex solvent extraction processes involving other organic solvents or mixtures (methanol, acetone), water or supercritical carbon dioxide. After extraction, the original (cellular) plant material is discarded. The type of solvent and extraction conditions used will govern the actual components that are extracted, and this can lead to variability between products made from the same herb[3]. Different solvent extracts will have divergent, but probably overlapping, chemical profiles. Ethanol-based tinctures are favored by many herbalists. They have the advantage of not supporting microbial growth and can be consumed directly; the amounts of ethanol involved are non-toxic. Tinctures can also be converted into alcohol-free glycerites, where the alcohol is removed by distillation and replaced with glycerin and flavorings to make a more palatable product, which nevertheless contains the same plant constituents as the original tincture. Where solvents other than ethanol or water are used, it is important to remove the solvent completely, and ensure the absence of any toxic solvent residues. Removal of solvent results in a 'dry extract' which is then available in powdered form. Dry extracts have the advantage of being concentrated forms of the herb, and are suitable for making more conveniently sized capsules and tablets for consumers. All extracts, whether wet or dry, will contain a narrower range of phytochemicals and in different relative proportions than the original herb. This is an important consideration when trying to compare the traditional uses and safety profile of an herb to that of a modern extract-based preparation.

*'Unorganized crude drugs'* i.e. those not containing plant organs, include volatile oils (e.g. peppermint oil), fixed oils (e.g. evening primrose oil), gums (e.g. acacia) and resins (e.g. myrrh). These may be sold in their original form (i.e. as liquids or solids) or incorporated into conventional dosage forms such as tablets and capsules.

The following plant-derived medicinal agents would not be considered as botanical products, as they consist of single chemical entities (SCE) and can be regarded as conventional drugs:

(1) SCE isolated from a plant, e.g. morphine or digoxin;
(2) SCE semi-synthesized from plant chemical, e.g. etoposide from podophyllotoxin;
(3) SCE chemical analogs of phytochemicals.

## REGULATION OF BOTANICAL PRODUCTS IN THE USA

An important factor which may compromise the safety and efficacy of individual botanical products is the level of regulation governing their manufacture and supply in the USA. While there is substantial legislation associated with conventional medicinal products, such as the requirement for Food and Drug Administration (FDA) registration

and guidelines on good manufacturing practice (GMP), the vast majority of botanical products are not marketed as medicines and such regulations do not apply. They are instead considered 'dietary supplements' and are governed by the 1994 Dietary Supplement and Health Education Act (DSHEA)[4]. Manufacturers are responsible for the veracity of health claims made on the label, but there is no requirement for any supporting evidence of efficacy to be submitted to the FDA[5]. Indeed, clinical trials on botanical products, if performed at all, usually occur after they have been marketed, and the FDA requires reporting only of adverse events[6]. In terms of safety, a dietary supplement is deemed unsafe if it presents a significant or unreasonable risk of illness or injury under the conditions of use on the label. There are some constraints on the claims that can be made for a product and all new product labels should be submitted to the FDA. However, under DSHEA, the burden of proof that a product is adulterated or unsafe rests on the FDA[7]. The Secretary of Health and Human Services may take action against a supplement that is unsafe or, in the case of a new dietary product, where there is inadequate documentation of safety[8]. Finally, although the manufacturer is responsible under DSHEA for controlling quality and safety, there is currently no legal requirement that they are produced according to the standards of GMP associated with medicinal products. Many products with limited quality controls find their way to the shelves of commercial outlets. However in March 2003, the FDA issued a draft GMP document on the production of dietary supplements for comment by those involved in the industry, and new legislation may be in place in the near future.

## THE LINK BETWEEN QUALITY, SAFETY AND EFFICACY IN BOTANICAL PRODUCTS

Despite evidence of efficacy for many herbal products, it is still not possible to be sure that all botanical products made from a particular herb will be effective, or even safe. Reproducible efficacy and safety of botanical products is based firmly on reproducible quality[9]. A goodquality product can be defined as one that is of the stated identity, free of noxious impurities and of the correct potency. Many manufacturers of botanical products are endeavoring to produce high-quality products that meet these criteria. However, a comparison between conventional medicines and botanical products will illustrate some of the particular difficulties associated with connecting quality to safety, and particularly to efficacy, in botanicals.

Conventional medicines are based on single chemical entities, and it is relatively straight-forward to achieve correct identity, purity and potency. For these medicines, extensive pre-clinical and clinical trials have established the precise dose range required for activity and characterized the safety profile of the active substance. In general, a conventional product that fulfils the above three parameters is virtually guaranteed to be efficacious and safe (i.e. exerting an acceptable benefit/risk ratio) in the majority of users.

Botanical medicines, however, pose a much greater challenge when it comes to assessing the quality of the product. The main issues are outlined in an article by Bauer[9] and include the following:

(1) Each herb or extract contains a multiplicity of phytochemicals, known and unknown, and there may be limited data on the actual phytochemical constituents responsible for the therapeutic effect, let alone their required concentrations in the plant material.
(2) The therapeutic effect of a plant extract may be due to synergistic, additive or even antagonistic effects of its various constituents[10], and so standardization of one or two constituents may not mirror efficacy.
(3) The amount of preclinical and clinical data on chemically defined botanical products is relatively limited, so it is difficult to assess the dose required for a therapeutic effect.
(4) The way the plant material was extracted affects the chemical profile of the product, hence herbal products made with different extraction methods and solvents can vary in their biological effect. Clinical data acquired with one extract are not directly applicable to another, i.e. the data are product- or extract-specific.
(5) Plant materials belonging to the same species can vary considerably in their phytochemical profile, depending on genetic and geographical factors and even on the age of the material and the conditions under which it was stored[3]. Therefore, merely using an herb of the correct identity in repeated batches will not guarantee an identical product, unless the chemical profile is matched from batch to batch. A recent study[11] on *Panax quinquefolius* L. (American ginseng root) showed that a sample grown in Illinois had a greater effect on brainstem neuronal activities than one grown in Wisconsin. This could be related to the relative ginsenoside profiles of the two samples.
(6) The type of contaminants found in plant materials (other botanicals, soils, microbes, environmental contaminants) are different from those encountered with single-chemical drugs and require special methods for their detection. This is significant from a safety point of view.

Therefore, even if a product of consistent quality can be produced—i.e. it contains the correct herb, free from adulterants and with specified levels of certain constituents—this is no guarantee of efficacy if reliable data linking specific constituents, doses and effectiveness are not available. On the other hand, for an herb with a recorded tradition of safe use, it may be possible at least to secure safety by ensuring correct identity, freedom from toxic impurities and contaminants and usage within the traditional dose range.

In an attempt to overcome the above issues, many manufacturers of botanical products are starting to produce standardized extracts[3,9] that are then used in clinical trials. In these, extracts are produced in a particular way and the content of a number of specified constituents is adjusted to within a narrow range or minimum value (Table 1[12]). Ideally, these are the known active constituents. However, it is usually the case that, as research on a particular herb continues, other constituents with relevant therapeutic activities are discovered and the standardization parameters change. An example is St John's wort, where early preparations were standardized only to hypericin, but more recent research has indicated a role for hyperforin in the activity of this herb and this, too, is now measured for standardization. Standardized products have the advantage of being made to a repeatable composition (in terms of the measured components) and are therefore favored for use in clinical trials.

Many advocates of traditional herbalism frown on this particular approach as standardization is often based on putative rather than proven active constituents and the final product contains only a partial and skewed chemical profile compared to the whole

herb that was used in traditional practice[13]. As a result of this view, and the costs involved in producing standardized products, a large number of non-standardized products are available for each commercially important herb. Alternatively, the extracts may be standardized to the same selected markers as the product that underwent a trial, but the other constituents may vary, owing to differences in the overall extraction method. These are probably not equivalent to the products on which trials have been published, and may not therefore produce the same therapeutic effect. Nevertheless, manufacturers rely on the publicity associated with the trialed

**Table 1** Examples of standardization parameters for herbal products. Reproduced with permission from Flynn R, Roest M. *Your Guide to Standardized Herbal Products.* Prescott, AZ: One World Press, 1995

| *Common name* | *Botanical name* | *Standardization parameter* |
|---|---|---|
| Garlic | *Allium sativum* | allicin or alliin (values vary) |
| Ginkgo | *Ginkgo biloba* | 24% ginkgoflavone glycosides, 6% terpene lactones |
| Kava | *Piper methysticum* | 30% kavalactones |
| St John's wort | *Hypericum perforatum* | 0.3% hypericin, 4% hyperforin |
| Valerian | *Valeriana officinalis* | 0.8–1% valerenic acid |

products to support sales of their version, which may not be therapeutically equivalent.

The issue of achieving bioequivalence in herbal products has been discussed in a review by Loew and Kaszkin[14]. This is relevant where trials have been conducted on a particular branded product, and other companies wish to demonstrate that their products will be equally efficacious. For extracts containing known active markers, they suggest that the concept of 'essential similarity' with respect to the levels of these substances can be applied. However, if the active components are not known, then data on selected chemical substances within an extract may not be sufficient to prove bioequivalence in terms of therapeutic effect, although the information may be useful to ensure repeatability of the production process. The authors suggest that equivalence should be shown in a range of aspects including pharmaceutical equivalence (chemical standardization), biopharmaceutical equivalence (*in vitro* dissolution rate) and comparable biological effects (*in vitro,* animal or clinical studies).

A number of studies comparing the bioequivalence of different brands of a particular product have been reported. Several silymarin preparations (derived from *Silybum marianum* or milk thistle) from the German market showed a two-fold difference in bioavailabilty (*in vitro* dissolution) between products[15]. Examination of a variety of ginkgo products available in the USA[16] showed clear differences in both the content of marker compounds and *in vitro* dissolution rates. Flavone glycosides ranged from 24 to 36%, the terpene lactones from 4 to 11% and ginkgolic acids from <500 to 90000ppm. The majority of products achieved the required dissolution rate of over 75% in 30 min. However, several fell short of this standard, one product achieving less than 25%

dissolution after an hour. Thus, even with the required chemical content, these products may fail to achieve therapeutic equivalence. Garlic showed dose-dependent effects in an *in vitro* enzyme assay—the inhibition of adenosine deaminase[17]. The authors suggested that this may be a useful test to demonstrate bioequivalence between products.

**Table 2** Methods of analysis specific to pharmacognosy. Adapted from references 18 and 19

| |
|---|
| Ash insoluble in hydrochloric acid (to measure inorganic impurities) |
| Foreign matter (to identify botanical and nonbotanical contaminants) |
| Stomata and stomatal index (to identify leaves) |
| Swelling index (to assess the polysaccharide content of gel-forming botanicals) |
| Water in essential oils |
| Foreign esters in essential oils |
| Fatty and resinified oils in essential oils |
| Odor and taste of essential oils |
| Residue on evaporation of essential oils |
| Solubility in alcohol of essential oils |
| Assay of 1,8-cineole in essential oils |
| Determination of essential oils in vegetable drugs |
| Pesticide residues |

## QUALITY CONTROL METHODS FOR BOTANICAL PRODUCTS

The analytical control of botanical products should ideally be based on approved methods and standards that are found in official monographs in pharmacopeias or other standards that have been validated. Where no 'official' monographs or standards exist, it is advisable for manufacturers to develop their own validated protocols. The standard or quality of an herbal product is determined, as mentioned earlier, by performing analytical tests to establish the identity of the plant material and/or its active principles, the content of active principles or characteristic marker compounds by assay and the purity of the product by exclusion of specific adulterants or contaminants. The methods employed for these aspects have been reviewed in detail by Forte and Raman[18] and are summarized here. Some of these methods are unique to the evaluation of botanical products (Table 2[18,19]).

The identification of whole crude drugs, i.e. plant material, is based on macroscopic appearance, organoleptic characters, microscopic appearance and presence or absence of characteristic chemical substances which may be determined by classical specific and non-specific 'wet tests'[20]. More specific chromatographic and spectroscopic techniques,

e.g. high-performance liquid chromatography (HPLC), thin-layer chromatography (TLC), gas chromatography (GC) and capillary electrophoresis (CE), or infrared (IR), nuclear magnetic resonance (NMR) and ultravioletvisible (UV-VIS) spectroscopy may also be applied[21] and are more appropriate for crude extracts. DNA fingerprinting has also been suggested as a means of identification, for example to distinguish between Korean ginseng *(Panax ginseng)* and American ginseng *(Panax quinquefolius)*[22].

In terms of determining the content of constituents, natural variation of crude drugs and the influence of processing make standardization more difficult than with synthetic compounds. Quantitative chromatography (HPLC or GC) is one of the most popular and effective means of quantifying compounds in crude drugs and their preparations. This may be combined with mass spectrometry to obtain more detailed information on the identity of the constituents analyzed[23]. Several other analytical methods may be used to quantitate herbal constituents[24] including separation and weighing of active constituents, titration, physical tests, quantitative spectroscopy, radioimmunoassay, enzyme-immunoassay and biological assays based on an appropriate therapeutic activity[25].

The analytical basis of the assay of a particular herbal product depends on the type of preparation and the state of knowledge about its active constituents[9]. Where the therapeutically relevant constituents are known, the product is standardized to that particular substance[9]. For example, St John's wort *(Hypericum perforatum)* is currently standardized with respect to both hypericin (0.3%) and hyperforin (4%), as these compounds have been associated with its biological activity. Alternatively, standardization may be based on a group of related constituents, all of which are known to contribute to therapeutic efficacy. An example here would be the measurement of total hydroxyanthracene glycosides in senna *(Cassia angustifolia or acutifolia)* fruit, as these compounds collectively provide the laxative effects of the botanical. When the active compounds are not known, the total native extract is regarded as the 'active principle' so that marker compounds that are specific for the botanical are used for quality control[9], e.g. parthenolide in feverfew *(Tanacetum parthenium)*. Alternatively, TLC, HPLC or gas-liquid chromatography (GLC) profiles are matched for repeatability. Single or multiple markers are used for internal batch control, to ensure that the concentration and ratio of components in an herbal mixture are present at reproducible levels in raw materials, manufacturing intermediates and the final dosage forms[21].

The purity of herbal products is an important consideration, as the adverse effects of botanical products have often been associated with substitution or contamination of the declared ingredients with a toxic substance such as a more toxic botanical, a poisonous metal or a potent non-herbal drug substance[26] (Table 3[18,26]). The determination of negative markers, e.g. in TLC, is employed to exclude the presence of extraneous herbal constituents. Simple visual examination will detect the presence of foreign material such as molds, insects and other animal contamination. Ash tests described in pharmacopeias give an indication of inorganic impurities present as contaminants in herbal specimens. The determination of the moisture content of crude drugs is particularly important for most plant materials, since these are susceptible to degradation or deterioration in the presence of excessive moisture. The contamination of herbal material with potentially pathogenic micro-organisms and microbial toxins provides a further hazard[26]. Standards for acceptable levels of microbial contamination in pharmaceutical preparations cannot always be attained with herbal products. Therefore, manufacturers will generally ensure

that, for crude drugs to be taken internally, the limits for bacterial and mold contamination as applied to foodstuffs are adhered to[24] unless the products are parenteral phytotherapeutic

**Table 3** Potential contaminants of herbal products. Adapted from references 18 and 26

| *Type of contaminant* | *Examples* |
|---|---|
| Toxic botanicals | *Atropa belladonna, Digitalis, Colchicum, Rauwolfia serpentina,* pyrrolizidine-containing plants |
| Micro-organisms | *Staphylococcus aureus, Escherichia coli, Salmonella, Shigella, Pseudomonas aeruginosa* |
| Microbial toxins | bacterial endotoxins, aflatoxins |
| Pesticides | chlorinated pesticides (e.g. DDT, DDE, HCH isomers, HCB, aldrin, dieldrin, heptachlor), organic phosphates, carbamate insecticides and herbicides, dithiocarbamate fungicides, triazin herbicides |
| Fumigation agents | ethylene oxide, methyl bromide, phosphine |
| Radioactivity | Cs-134, Cs-137, Ru-103, I-131, Sr-90 |
| Metals | lead, cadmium, mercury, arsenic |
| Synthetic drugs | analgesic and anti-inflammatory agents, corticosteroids, hydrochlorothiazide, diazepam |
| Animal drugs | thyroid hormones |

preparations[26]. Pesticides and fumigation agents can also be tested by chromatographic and other means[24,26,27]. Methods can also be applied to determine the presence of residual levels of radioactivity and toxic metals[18,26].

## EVIDENCE FOR EFFICACY OF BOTANICAL PRODUCTS ACTING ON THE NERVOUS SYSTEM

The numerous botanical products available to consumers include several that have become popular for their potential use in conditions with a neurological basis. Principal examples are ginkgo leaf *(Ginkgo biloba)* for improvements in cognitive function, St John's wort herb *(Hypericum perforatum)* for the treatment of mild to moderate depression, valerian root *(Valeriana officinalis)* for insomnia and kava root *(Piper methysticum)* to relieve anxiety. Chinese or Korean ginseng *(Panax ginseng)* is also reputed to improve cognitive function. Jensen[6] cited poor patentability, uncertainty about active compounds and unknown pharmacodynamics (i.e. mechanism of action) as the main drawbacks in running trials on botanical products. However, human studies of varying levels of reliability have been performed on these herbs and reviews and meta-

analyses are available. The scope and value of these compilations is often compromised by the limited quality of some of the studies available. Tables 4 and 5[28,29] outline guidelines provided by European and US authorities on the evaluation of published data relating to the safety and efficacy of botanical products. Meta-analyses of randomized, controlled trials are suggested to be the best level of evidence.

Systematic reviews and meta-analyses of ginkgo in the late 1990s showed a superior effect to placebo in delaying cognitive deterioration in dementia[30] and modestly improving cognitive function in Alzheimer's disease[31]. This supports earlier reviews showing clear evidence in favor of overall improvements in cognitive function and symptoms such as forgetfulness and poor concentration[32]. One meta-analysis cautiously concluded that ginkgo was superior to placebo in individuals with cerebral insufficiency[33]. By contrast, a recent study[34] reported no improvement in memory or cognitive function in healthy, elderly people receiving a standard dose of ginkgo for 6 weeks. However, one contributing factor here may be that the treatment period was shorter than those used in earlier studies.

**Table 4.** Factors that increase the relevance and credibility of published data. Based on FDA May 1998: *Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products* and references 28 and 29

| |
|---|
| Multiple studies conducted by different investigators and/or independent literature reports where the findings are consistent |
| A high level of detail in the published reports, including clear and adequate descriptions of statistical plans, analytical methods and study endpoints, and a full accounting of all enrolled patients |
| Appropriate endpoints that can be objectively assessed and are not dependent on investigator judgment (e.g. overall mortality, blood pressure, or microbial eradication rather than 'relief of symptoms') |
| Robust results achieved by protocol-specified analyses that yield a consistent conclusion of efficacy and do not require selected *post hoc* analyses such as covariate adjustment, subsetting, or reduced data sets (e.g. analysis of only responders or compliant patients, or of an 'eligible' or 'evaluable' subset) |
| A conduct of studies by groups with properly documented operating procedures and a history of implementing such procedures effectively |

**Table 5.** Definitions of the levels of evidence of the safe and effective use of an herbal medicinal product. Based on the US Agency for Health Care Policy and Research and the WHO and references 28 and 29

| *Level* | *Type of evidence* |
|---|---|
| Ia | Evidence obtained from meta-analysis of randomized controlled trials |
| Ib | Evidence obtained from at least one randomized controlled trial |
| IIa | Evidence obtained from at least one well-randomization designed controlled study without |
| IIb | Evidence obtained from at least one other type of well-designed quasi-experimental study |
| III | Evidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies and case-control studies |
| IV | Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities |

A 2002 Cochrane review[35], while recognizing the need for more clinical trials, concluded that there was promising evidence of improvement in cognition and function associated with ginkgo, with no excess side-effects compared to placebo.

Meta-analyses of St John's wort[36–39], controlled trials against tricyclic antidepressants[40,41] and selective serotonin release uptake inhibitors[42,43] and a Cochrane review[44] have all concluded that this botanical is superior to placebo and of similar effectiveness to conventional antidepressants in treating mild-to-moderate depression.

A systematic review of the relatively small number of placebo-controlled clinical trials of kava for anxiety symptoms found a significant beneficial effect of the herb[45]. The therapeutic potential of kava for anxiety, including its putative mode of action, is the subject of a recent review[46]. However, there have been some recent safety concerns with this botanical that may limit its use (see later)[46].

In the case of valerian, a systematic review of nine trials found that there was favorable but not compelling evidence in support of an effect in insomnia[47.] For Korean ginseng, a systematic review of randomized clinical trials concluded that the efficacy of the root extract could not be established beyond reasonable doubt for cognitive improvements or various other therapeutic claims[48]. However, a recent conference report stated that Chinese ginseng was more effective than Duxil® (Servier International, France) (almitrine plus raubasine) in improving memory function after stroke[49].

Other, less well-studied, botanicals with promise in improving cognitive function include the ayurvedic herbs *Bacopa monniera*[50] and *Centella asiatica*[51] and the European herb *Salvia lavandulaefolia*[52]. The narcotic plant *Cannabis sativa* is also receiving considerable interest for its potential use in treating multiple sclerosis[53,54]. However, owing to legal restrictions, it is unlikely that any products from this botanical will be freely available as non-prescription items.

## SAFETY OF BOTANICAL PRODUCTS—ADVERSE REACTIONS AND INTERACTIONS

A large proportion of the general public has the misconception that herbal products are safe because they are of natural origin. While sensible use within the recommended dosage is generally safe for most traditional herbs, adverse reactions may arise from the inherent properties of the herbal ingredients, from misuse, abuse and overuse of products, or from misidentification of plants or adulteration of products. A particularly serious example, reported from Belgium[55], involved the substitution of the Chinese herb *Aristolochia fangchi* into slimming pills purportedly containing *Stephania tetrandra.* The two herbs are considered interchangeable in traditional Chinese medicine, but whereas the latter herb is relatively innocuous, the former contains nephrotoxic and carcinogenic aristolochic acids. Women ingesting these pills developed moderate to end-stage renal disease resulting from renal interstitial fibrosis and urothelial carcinoma, eventually requiring treatment by renal dialysis or transplantation. Chinese herbal medicines have sometimes been found to be adulterated with undeclared synthetic drugs[56]. Examples of adverse events involving herbal products have been summarized in review articles[5,26,29,56]; some case reports from the USA are summarized in Table 6[29,57–69].

There are certain categories of persons who are at a higher risk of toxic effects of herbs, owing to their altered pharmacokinetic profiles and drug metabolizing capability from the norm[70]. These include fetuses, babies, the elderly, those with pre-existing illness and those who are malnourished. Gender and racial differences may also be significant in this context. Toxicity is also more likely in users of botanical products with long-term use, consumption of amounts exceeding recommended levels and simultaneous use of many herbal products and conventional drugs.

An important source of adverse events is drug-herb interactions. Adverse effects may occur from either pharmacodynamic interactions—with the drug and botanical acting on similar or opposing pharmacological targets—or pharmacokinetic interactions, where, typically, consumption of the botanical causes alterations in the metabolism and pharmacokinetic profile of the conventional drug. The potential for such interactions is receiving more attention, owing to recognition of the extent of usage of botanical products, combined with a growing number of case reports of relevant events. These are particularly significant where the drug involved has a low therapeutic index—for example, anticoagulants—or failure of therapy may have life-threatening consequences (as with immunosuppressant or anti-viral drugs). In one study[71], consumption of St John's wort reduced the area under the curve for indinavir (an HIV-1 protease inhibitor) by 57%, a large enough magnitude potentially to render the treatment ineffective.

A detailed description of all documented interactions is beyond the scope of this chapter. For more information, the reader is referred to the many reviews on potential and actual drug interactions with herbal products that have been published[5,72–78]. One review focused particularly on potential drug-herb interactions in patients with dementia[79], whilst another article discussed herbal interactions with anti-psychotics, antidepressants and hypnotics[80].

Anticoagulants are an important group of drugs with low therapeutic index that are of particular concern when considering drug-herb interactions. Heck[81] reviewed alternative remedies with potential or reported interactions with warfarin. Popular herbs or

**Table 6.** Examples of case reports from the USA of toxic effects of herbal remedies. Adapted from reference 29

| *Herbal preparation* | *Cause of toxicity* | *No. of cases* | *Toxic effects* | *Reference* |
|---|---|---|---|---|
| Chaparral, oral capsules | chaparral *(Larrea tridentata)* | 1 | severe hepatitis leading to end-stage hepatic failure; liver transplant | 57 |
| Oral preparation | pennyroyal (leaves of *Mentha pulegium* or *Hedeoma pulegioides* containing pulegone) | 4 | hepatotoxicity, CNS symptoms, abdominal cramping, or hypotension and tachycardia | 58 |
| 'Ultimate Xphoria', oral preparation | *Ephedra sinica* | 1 | cardiac arrhythmias leading to death | 59 |
| Dietary supplement for 'internal cleansing' as part of a 'program', oral tablets | *Digitalis lanata* identified in plantain | 2 | severe vomiting, palpitations, atrioventricular block | 60 |
| 'Jin Bu Huan Anodyne Tablets' (CHR), oral tablets | contained L-tetrahydro-palmatine present in genus *Stephania;* mislabeled as *Polygala chinensis* | 13 | 3 cases of acute toxicity in infants—lethargy, respiratory depression, bradycardia, hypotension 10 cases of chronic toxicity in adults—acute hepatitis | 61, 62, 63 |
| 'Paraguay Tea', oral preparation | contained belladonna alkaloids: atropine, scopolamine, hyoscyamine; should contain caffeine or theophylline | 7 | anti-cholinergic effects: dry skin, hyperthermia, tachycardia, hallucinations, agitation, dilated pupils | 64 |
| Oral preparation | contained *Podophyllum peltatum;* mistaken for *Mandragora officinarum;* both herbals commonly known as mandrake | 1 | severe vomiting | 65 |
| 'Tung Sheh' (CHR), oral pills | contained undeclared mefenamic acid and diazepam | 1 | acute interstitial nephritis | 66 |
| 'Gan Mao Tong Pian' (CHR), oral | contained undeclared phenylbutazone | 1 | aplastic anemia due to phenylbutazone | 67 |

| | | | | |
|---|---|---|---|---|
| tablets | chlorpheniramine and diclofenac | | | |
| 'Cow's Head brand Tung Shueh', oral tablets | contained indomethacin, mefenamic acid, diclofenac and diazepam | – | none reported. Products confiscated by Drug Enforcement Agency, USA owing to illegal importation | 62 |
| 'Nutrien' (CHR), oral liquid | contained lead and thallium | 2 | alopecia and sensory polyneuropathy due to thallium | 68 |
| Herbal balls (CHR), oral preparations | nine samples contained arsenic and mercury; 1 sample contained arsenic | – | none reported. Samples collected for random analyses | 69 |

CHR, Chinese herbal remedy; CNS, central nervous system

supplements causing an increased risk of bleeding or possible enhancement of warfarin's effects include feverfew, garlic, ginger, ginkgo, horsechestnut, red clover, devil's claw, dong quai *(Angelica sinensis)* and vitamin E. Ginseng, coenzyme Q10 and green tea (in large amounts) are suggested to decrease warfarin's effects. Where such interactions are taking place, it is important to institute gradual rather than abrupt withdrawal of the herb.

Some studies have focused on evaluating the extent of the potential for drug-herb interactions in various patient populations. In one study on ambulatory, geriatric hospital patients ($n$=182), about 46% reported taking a CAM product with anticoagulant properties and half of these were also on prescribed anticoagulants. However, very few patients' charts had any record of the CAM product in use, suggesting that physicians either did not question the patients on CAM use, or did not consider them significant enough to record[82].

A Canadian study[83] of 195 older adults (aged 65 years or over) attending a memory clinic found that about 27% were current or past users of herbal medicines. The most frequently used herbal medicines included ginkgo and garlic, both of which are known to affect hemodynamic parameters[81]. Based on scientific literature on drug-herb interactions, the researchers identified nine patients in whom potential interactions might occur, including those between ginkgo and aspirin, ginkgo and trazodone, ginseng and amlodipine, and valerian and lorazepam[83].

The use of botanicals by patients presenting for surgery is also of concern, as some drug-herb interactions may lead to hemodynamic instability[81]. A survey involving about 750 patients in Texas presenting for pre-anesthetic evaluation prior to surgery[84] found that about 500 used at least one nutraceutical agent. These included garlic preparations (43%), ginkgo (32%), St John's wort (30%) and Ma Huang (18%)—a source of ephedrine. A similar study in the UK[85] involving almost 3000 patients found that about 5% (131) were taking one or more herbal remedies, but this was only recorded in two cases. Again, garlic, ginkgo and St John's wort were among the most commonly used herbal products. Hence, close questioning regarding use of botanicals in those patients recommended or presenting for surgery is important for taking appropriate remedial measures. It has been suggested that the taking of all herbal remedies should cease 2 weeks before surgery[86].

The botanicals acting on the nervous system that were discussed earlier (ginkgo, St John's wort, kava, valerian and ginseng) have all been associated with adverse effects and/or interactions. In the past few years, there have been about 35 case reports of severe liver toxicity associated with kava intake in Europe and the USA[5].

The two US cases are described in detail in a recent *Journal of the American Medical Association* article[87]. Although there is a view that a direct causal relationship to kava has been difficult to establish in many of the cases[46], the reports have led to a ban on kava-containing medicinal products in the UK[88,89]. Other side-effects, possibly involving drug interactions, related to kava use include one case of neurotoxicity/convulsions and another of lethargy and disorientation in a patient also receiving alprazolam, cimetidine and terazozin[5]. Izzo and Ernst[77] report an increase in 'off periods' (periods when the drug therapy fails to work) in Parkinsonian patients taking levodopa who consumed kava preparations.

There have been four case reports of multiherb preparations containing valerian causing hepatitis and jaundice[90], although causality is difficult to establish in this type of preparation. A constituent of valerian herb, valerenic acid, is known to inhibit the breakdown of the neurotransmitter GABA. Thus, there is a potential pharmacodynamic interaction with the benzodiazepine class of drugs.

A systematic study[91] of adverse events associated with Korean ginseng found that the most commonly experienced effects were headache and sleep or gastrointestinal disorders. However, their incidence was no greater than for placebo. Combination products have led to more serious adverse events, although in such cases causality is more difficult to determine. Possible interactions were reported with warfarin, phenelzine and alcohol.

In addition to some gastrointestinal sideeffects, the main safety issue with ginkgo is its ability to reduce blood coagulation. There have been reports of internal bleeding associated with ginkgo alone, as well as in combination with aspirin, rifecoxib and warfarin[5]. There are also reports of raised blood pressure when ginkgo was combined with a thiazide diuretic, and coma in a patient also taking trazodone[77]. Two patients with well-controlled epilepsy presented with recurrent seizures 2 weeks after starting to take ginkgo extract. The patients were seizure free after discontinuation of the ginkgo product[92].

Of all these botanicals, St John's wort has been associated with the greatest number of adverse effects[5,77]. An important constituent, hypericin, has the potential to cause phototoxicity, although this has mostly been observed in patients undergoing ultraviolet or laser therapy. Other reports that may be linked to consumption of St John's wort include mania, psychotic relapse in a schizophrenic patient, serotonin syndrome-like events, adverse effects during anesthesia and elevated thyrotropin levels. An important source of pharmacodynamic interactions is with serotonin-reuptake inhibitors, which can lead to central serotonin syndrome. The induction of cytochrome P450 enzymes CYP1A2, CYP2C9 and CYP3A4 as well as P-glycoprotein[78] following administration of this botanical for more than 2 weeks is known to lead to the reduction in plasma levels, and hence efficacy, of a number of drugs. Such interactions have been reported with cyclosporin, amitriptyline, digoxin, indinavir, warfarin, phenprocoumon and theophylline. Intermenstrual bleeding was reported in oral contraceptive users[5,77]. A systematic review[93] of drug interactions with St John's wort has identified clinically

significant interactions with warfarin, phenprocoumon, cyclosporin, HIV protease inhibitors, theophylline, digoxin and oral contraceptives. In Sweden and the UK, the potential risks to patients were judged to be significant, and product information of the licensed medicines involved has been amended to reflect these concerns[93]. In a small study involving five patients[94], St John's wort (900 mg daily for 18 days) surprisingly led to a reduction in the levels of the active metabolite (SN-38) of the anticancer drug irinotecan, a known substrate of CYP3A4.

Botanical medicines cannot, therefore, be considered safe in all circumstances. In considering the potential risk to consumers of an adverse effect from a botanical product, it is important to note that most of the published evidence for toxicity of herbal products consists of a single or a few case reports. A causal relationship between the product or an ingredient and an adverse event may not always be established with certainty[95]. The multi-ingredient nature of some herbal products means that it is not always possible to relate toxic effects to a specific herbal component. Therefore, such reports must be assessed with caution[95]. Nevertheless, there have been sufficient reports of adverse effects and drug interactions in the literature to indicate that problems can and do arise. Where drug-herb interactions have been identified for botanicals, it is prudent to question and instruct patients accordingly.

## CONCLUSIONS

There is a significant amount of evidence to suggest that botanical products may be of use in treating neurological disorders and other conditions requiring an effect on the nervous system, e.g. depression, anxiety or insomnia. At the present time, a wide variety of non-equivalent and non-standardized products are commercially available for a given botanical, so that it is not easy to decide whether or not a given product will be effective. This is a function of both the relatively low level of regulation of these products, and the lack of information on active constituents and doses that would support the manufacture of products with validated efficacy. In general, their effects may be considered as mild, compared to those of conventional drugs. However, the potential for adverse effects and interactions with conventional drugs must not be over-looked. It is important that clinicians question and counsel their patients on their use of botanical products, so that such events can be prevented.

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# 3
# Chiropractic

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*Complementary Therapies in Neurology: An Evidence-Based Approach*
Edited by Barry S.Oken
ISBN 1-84214-200-3 

## INTRODUCTION

Manual therapies have been practiced in virtually all societies and cultures throughout recorded history. In Western civilization, its practice is recorded in the works of Hippocrates as well as Galen and has survived to the present in various forms in different societies. In some countries, such as Japan, the majority of practitioners of spinal manipulation are lay practitioners, while in Europe a large percentage are medical physicians who have additional training in the practice. In North America, some medical and osteopathic physicians offer spinal manipulation. There is also a growing (but still small) group of physical therapists practicing spinal manipulation. Although the osteopathic profession was the first in the USA to organize a body of knowledge in the practice, the great majority of osteopaths today do not practice manipulation. At this point in time chiropractors provide the vast majority of these services in North America as well as in many other parts of the world, and are equated in the public perception with the practice of spinal manipulation. Currently, well in excess of 90% of spinal manipulations in the USA are delivered by chiropractors[1]. They also provide a growing percentage of these treatments in Japan, Australia, New Zealand, South Africa and many parts of Europe. This chapter concerns itself with the current state of chiropractic, focusing on its place in the health-care system in the USA.

Chiropractic traces its roots to Daniel David Palmer, a magnetic healer and sometime school-teacher in the Midwest. He was exposed to the ideas of various practitioners who employed manual therapies (bone-setters, lay practitioners and maverick medical physicians) and organized these skills into the profession of chiropractic. The first official chiropractic treatment, described by Palmer as a spinal adjustment, was performed in 1895 in Davenport, Iowa. This first treatment was described by Palmer as the reduction of a prominence in the upper thoracic spinal region of a janitor named Harvey Lillard. This man, who had been profoundly deaf, claimed return of hearing following treatment. Palmer eventually opened his first chiropractic school in Davenport, where it exists to this day. Flamboyant and excessive claims by early chiropractic leaders led to serious conflicts with mainstream medical practitioners that persisted throughout the first 80 years of chiropractic history.

Several milestones have been important in understanding the relationship between the chiropractic profession and medicine. These include a conference that was organized

under the auspices of the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) at the instruction of the US Congress in 1975. This conference, entitled *The Research Status of Spinal Manipulative Therapy*[2], brought together many experts from the medical, chiropractic and scientific communities to examine the state of research into spinal manipulation and to chart directions for future study. Much of the progress in the validation of spinal manipulation can be traced to this conference. Another noteworthy milestone included changes to the American Medical Association code of ethics that had previously proscribed interactions between chiropractors and medical doctors. This change only occurred after a lengthy and rather bitterly fought lawsuit, but has been followed by an era of unprecedented growth in professional relationships between chiropractors and medical professionals. Recent recognition of the large number of Americans utilizing complementary and alternative therapies[3,4] hasmotivated significant interest on the part of policy makers as well as physicians. This interest prompted the development of the Office of Complementary and Alternative Medicine within the National Institutes of Health. This office has grown into the National Center for Complementary and Alternative Medicine. These and other developments have led to greater interaction and increasing co-operation between medical physicians and chiropractors, as well as increased curiosity regarding the training, theories and practices of these practitioners.

## UTILIZATION

The growth of chiropractic services pre-dates the recent explosion of interest in complementary and alternative approaches to healing and health maintenance. However, its recent growth must be viewed in the context of the expanded use of all forms of complementary and alternative medicine (CAM) therapies in the USA. This was clearly illustrated by systematic surveys in 1990 and repeated in 1997 by Eisenberg and colleagues[3,4]. Theseresearchers were the first systematically to demonstrate the high levels of use of CAM therapies by the public at large and they also illustrated a significant growth over this relatively short period. In 1990, 33.8% of the adult population in the USA reported using one or more CAM therapy, while by 1997, this figure had grown to 42.1%. Not only was use of CAM therapies increasing, but the probability of visiting a CAM provider increased (from 36.3% in 1990 to 46.3% in 1997). Their findings indicate a 47.3% increase in the number of visits to alternative medicine practitioners over this brief interval of 7 years. Expenditures on these therapies also increased (by 45.2%, according to their estimates). It is somewhat astounding to realize that a conservative estimate of these expenditures amounted to $27 billion in 1997, a figure that is comparable to the projected out-of-pocket expenditures for all US physician services.

In the survey by Eisenberg and co-workers, the single most popular CAM intervention was relaxation therapy. However, chiropractic followed close behind and represented by far the largest group of alternative providers frequented by the general population[4]. It is clear that both the number of patients frequenting chiropractors and the number of chiropractic visits per capita have markedly increased in the past 15–20 years. In 1980, the US Department of Health, Education and Welfare reported that about 3.6% of the

population received a chiropractic treatment each year, and that the number of individual treatments amounted to 62 visits per 100 person-years[5]. A survey in 1990 reported that 10.1% of the population consulted a chiropractor within the preceding year[3], and this number had grown to 11.0% by 1997[4]. Estimates based on data collected from the late 1980s to 1991 determined that there were about 100 visits to chiropractors per 100 person-years[6].

Medical practitioners, including neurologists, can anticipate that many of their patients have recently been treated by, or are likely to seek the services of, a chiropractor during the course of their care. It is therefore of growing importance to have some knowledge of chiropractic, including the training and background of its practitioners, its theoretical basis and the research relative to its use, in order to advise patients appropriately.

## THE STATUS OF THE PROFESSION

Chiropractic enjoys greater recognition, utilization and integration into the health-care system than any other CAM profession. Over the past 100 years, chiropractic has become an organized profession with licensure to practice as a primary contact health-care profession in every state in the USA and all Canadian provinces as well as many other countries around the world. Chiropractic colleges and universities now have accredited educational programs of study, described in the following section. The National Board of Chiropractic Examiners administers the basic science, clinical science, case management and practical examinations that are required by all states in order to obtain a license to practice. A similar licensing board exists in Canada, and licensing agencies exist in countries such as the UK, the Scandinavian countries, Australia, New Zealand, South Africa and many others.

More than anything, however, the growing integration of chiropractic into the mainline health-care system is due to the dual effects of increased numbers of patients seeking such care and the growing number of studies, both clinical and basic science, supporting a positive effect of spinal manipulation. The emerging emphasis on ‘evidence-based’ health care and on patient satisfaction and cost containment has further advanced interest in chiropractic as an alternative treatment for a number of conditions, some of which respond poorly to conventional medical care. The growing body of evidence of effectiveness of spinal manipulation for several indications has culminated in the inclusion of manipulation among a very short list of recommended therapies in evidence-based guidelines published in the USA[7], Canada[8], and the UK[9]. These have resulted in an increase in the integration of chiropractic and spinal manipulation into pain clinics, spine centers and managed care systems.

Along with an increasing use of manipulative therapy has come a dramatic increase in the number of chiropractors. From an estimated 13000 practitioners in 1970, the number had grown to around 50000 by 1994. This represents approximately one chiropractor for every 5000 residents in the USA. A recent study anticipated that the number of chiropractors will double again by the year 2010 to over 100000[10]. These numbers become all the more remarkable when contrasted with the projection that the number of medical physicians will grow only by an estimated 16% over the same period. This

indicates that chiropractors will constitute a growing segment of the health-care system in the near future.

The development of chiropractic has not been confined to North America. The World Federation of Chiropractic (WFC) has representatives from 80 countries and is recognized as a Non-Governmental Organization within the World Health Organization (WHO). Since 1993, the WHO has co-sponsored the academic program at the biannual congress of the WFC. The WFC is also a member of the Council of International Organizations of Medical Sciences of the WHO. There are now colleges of chiropractic in Canada, Australia, New Zealand, several European countries, South Africa, Japan, Mexico and Brazil. Most of the colleges outside North America are components of government-sponsored universities and colleges.

## EDUCATION

Over the past century, chiropractic education evolved from a limited, 8-week course of study at the turn of the century to a full-fledged course of study lasting 4–5 academic years, preceded by 3–4 years of undergraduate education. It would not be an exaggeration to say that success in the development of chiropractic education has played a large part in the growing acceptance of chiropractic as a profession.

There have been several important milestones in the development of chiropractic education. None was more important than the recognition of the Council on Chiropractic Education (CCE) as the accrediting agency for chiropractic education by what was then the US Office of Education (now the US Department of Education) in 1974. The CCE established a minimum standard for admission and pre-professional requirements as well as prescribing minimum standards for facilities and the course of study in accredited chiropractic teaching institutions. Current standards require that all prospective students have a minimum of 2 years of pre-professional education, with specific requirements in the sciences and a minimum grade point average (GPA). Increasingly, individual colleges require a bachelor's degree for admission. The course of study in chiropractic schools is 4–5 academic years, with much of the final year being devoted to training in a supervised clinical setting (with defined standards for this clinical experience). The first 3–4 years of the program is evenly divided between the basic medical sciences and the clinical sciences.

Currently, there are 14 accredited chiropractic colleges in the USA. An accreditation process, under the direction of the CCE, with periodic reaccreditation, ensures that colleges continue to meet these standards. Many chiropractic schools have also received accreditation from their regional post-secondary accreditation body, permitting them to grant undergraduate degrees based on their course of basic science instruction. The CCE has also been instrumental, through involvement with the Councils on Chiropractic Education International, in helping to establish minimum education standards in other parts of the world.

Under the guidance of the CCE, the great majority of the basic sciences are taught by professors with advanced degrees in the particular area of study. Most of the clinical sciences are taught by chiropractors, although there is a growing educational involvement of medical physicians and individuals with dual degrees. Additionally, an increasing

number of chiropractic students are receiving part of their clinical experience in medical facilities.

The great majority of chiropractic students take a national board examination that is administered under the auspices of the National Board of Chiropractic Examiners (NBCE), which was established in 1963. This examination consists of a basic science part, a clinical part, a problem-solving portion and a practical examination. Most states currently require passage of this examination prior to licensure.

## LICENSURE

Chiropractic licensure is the responsibility of each state, subject to its own chiropractic practice act and the interpretations of that law. Therefore, there is some variability between states in the licensure requirements. Although the great majority of states require graduation from a chiropractic school accredited by the CCE, the role of the National Board examination in licensure varies. Many states require their own examination, often in addition to the National Board, prior to licensure. Furthermore, the requirements for postgraduate continuing education vary from state to state.

All states permit direct access of patients to chiropractors as portal-of-entry providers. In the great majority of states, chiropractors are permitted to employ diagnostic measures necessary to ensure the suitability of patients for treatment. This includes the performance of physical examination procedures and the interpretation of laboratory tests. Most states also permit chiropractors to maintain and use radiological facilities. To a large extent this is the result of a long-standing boycott of chiropractors by radiologists who would not perform radiological tests at their request. The more recent co-operation between these professions has led to a decrease in the number of chiropractic offices maintaining their own radiographical facilities. Chiropractic schools have historically devoted a significant amount of training to the study of radiology, and studies have shown that the ability to interpret X-rays for pathological red flags by chiropractors is at least as good as that of family physicians and orthopedic residents and specialists[11].

Despite the relative uniformity of chiropractic laws, there remain a few states where chiropractors are permitted to recommend or prescribe medications and perform minor surgical procedures, and other states where they are not even permitted to perform such procedures as a prostrate physical examination. Most of these practice variations fly in the face of education, which has become increasingly uniform as the result of national accreditation.

## SPECIALTIES

The chiropractic profession has several established specialty councils, most of which have a diplomate or certification process. These councils are established under the auspices of the American Chiropractic Association (ACA) and/ or the International Chiropractic Association (ICA) to recognize and encourage greater expertise in particular disciplines. At the present time, recognized programs include radiology, orthopedics, sports medicine, rehabilitation, industrial medicine and nutrition.

With the exception of the diplomate program in radiology, which has an established 2year residency, most of these programs consist of postgraduate courses of at least 300 h (diplomate programs) or 100 h (certification programs) of study in the field. There are qualification examinations required at the end of these programs.

## SCOPE OF PRACTICE

State law and the legal interpretations of the law define the scope of chiropractic practice. As described above, there is some variability in the diagnostic and therapeutic interventions that are permitted from state to state, but in most locations these include the diagnostic procedures that are required to determine the appropriateness of patients for chiropractic care. In all states, chiropractors are allowed to see patients without referral from other physicians and to treat them within the scope of the law.

Most state laws do not restrict the type of patients that can be seen and treated by chiropractors. On a practical level, however, the vast majority of patients seen by chiropractors are treated for musculoskeletal conditions, with only a very small percentage seen primarily for conditions that would commonly be consid ered to be internal disorders[6,12]. Historically, exaggerated claims of therapeutic efficacy on the part of some chiropractors, particularly regarding treatment of various non-musculoskeletal conditions and diseases, has been a major impediment to good relations between chiropractors and medical physicians. There are many anecdotal descriptions of successful chiropractic treatment of various internal disorders scattered within the chiropractic (and, indeed, osteopathic and medical) literature. The few attempts at systematically evaluating these claims (particularly with regard to the treatment of asthma and colic) have not provided any dramatic support for spinal manipulation in these conditions (see below).

Surveys and reviews of records of chiropractic offices[6,12] havefound that the majority of chiropractic patients are seen for complaints of low back pain. Neck pain is the next most common presenting complaint, with headache (cervicogenic and otherwise) following. Many of these patients presenting with these conditions have additional diagnoses and a wide variety of general symptoms. Improvement in these additional symptoms during the course of chiropractic treatment has provided much of the impetus for anecdotal claims of benefit in the treatment of other conditions, including internal disorders. The three most frequently diagnosed non-musculoskeletal complaints treated by chiropractors are asthma, otitis media and migraine headaches. These conditions, however, accounted for only one in 200 patients. Only a very small percentage (1–10%) of patients seeking chiropractic care do so for non-musculoskeletal symptoms. Given these statistics, it is somewhat ironic that overzealous claims made by some chiropractors concerning the treatment of a tiny fraction of chiropractic patients produce the greatest amount of friction between chiropractors and the medical community.

The strongly musculoskeletal bias of the conditions presenting to chiropractic offices probably results from the fact that patients are most likely to view chiropractors as being particularly effective in the treatment of these conditions. This distribution of patients may also result from the fact that conditions such as back and neck pain are often refractory to conventional medical care. It is not surprising, then, that the greatest amount

of evidence for a beneficial effect of chiropractic and spinal manipulation is in the treatment of back pain, neck pain and headache (see below and Chapter 15.

Historically, most chiropractic patients saw medical physicians first, and only sought chiropractic care when all else failed. Increasingly, this is now not the case. Therefore, the quality of chiropractic education in the primary analysis and diagnosis of patients has become of greater importance.

## REIMBURSEMENT

The nature of reimbursement for chiropractic services has changed, along with the maturation of the chiropractic profession and the fact that the general population has increasingly viewed chiropractic as a viable alternative or adjunctive method of treatment. To some extent, changes in reimbursement patterns have also been driven by trends in medicine as well as social and reimbursement policy in general.

Up to the 1960s, the vast majority of chiropractic treatments were provided on a fee-for-service basis. One milestone in the movement away from this was the inclusion of chiropractic in the original Medicare law. This inclusion was legislated in a rather narrow fashion and with tight restrictions on issues ranging from the types of conditions to be treated and the reimbursements provided. Nonetheless, it provided some impetus towards incorporation of chiropractic services in other third-party payer systems. However, through the 1970s and early 1980s transition to third-party payment proceeded at a slow pace with inclusion of chiropractic services in worker's compensation programs and many private insurance programs. Since chiropractors were often involved in treating patients with neck and back injuries, there was also involvement in the personal injury arena.

With the more recent growth of health maintenance organizations (HMOs), there has been slowly evolving inclusion of chiropractors in many of these plans. Some have restricted access strictly on the basis of referral from primary care providers, while a growing number of plans permit self-referral, usually under a system of strict guidelines for numbers of treatments.

Integration of chiropractic into the US armed services is proceeding after the conclusion of a pilot program exploring the feasibility of such involvement. Additionally, the US Veterans Administration health-care system will be incorporating chiropractors, although the precise nature of this involvement is still being established.

In the early 1990s the primary sources of payment for chiropractic services included private insurance and direct payments from the patient[6]. Together these were estimated to comprise 60% of chiropractic payments. Worker's Compensation and automobile accident insurance accounted for an additional 10–15% each, and Medicare represented another 8%. Other forms of payment, including Medicaid and managed care, contributed the remaining 10%. However, with the growing integration of chiropractic services into managed care, the portion related to HMOs is expected to grow significantly[10].

## ALTERNATIVE, COMPLEMENTARY OR MAINSTREAM?

There has been considerable debate, both inside and outside the profession, regarding the role(s) chiropractors should play in the health-care delivery system. The most common way in which chiropractors practice is as limited musculoskeletal specialists, dealing primarily with painful conditions either independently or, increasingly, as part of an interdisciplinary team. There are those within the profession who advocate chiropractors as primary health-care gatekeepers with a particular emphasis on ambulatory musculoskeletal conditions. There are some chiropractors still advocating a broad practice as general primary (alternative/complementary) health-care providers not limited to musculoskeletal conditions[13,14]. Although all three of the sepractice models can be found within the chiropractic profession, all studies have shown that chiropractors treat a limited array of conditions, with up to two-thirds of patients presenting with low back pain[6,12,15].

Chiropractic has become so commonly utilized and tightly woven into the fabric of health care in the USA that some have argued that it has entered the health-care mainstream[14,16–18]. Indeed, there are a growing number of examples of integration of chiropractic services into medical clinics and HMOs. Chiropractors are permitted membership in all major spine societies including the North American Spine Society, the American Back Society and the International Society for the Study of the Lumbar Spine, and there is a recently formed society specifically to encourage co-operation between chiropractors and neurosurgeons.

Even when chiropractic services are not performed as an integrated part of medical care for their condition, most patients utilize chiropractic services in combination with traditional medical care. Therefore, it has become increasingly common to refer to chiropractic as ‘complementary’, rather than ‘alternative’[19–21]. It is important to note that many patients with common neurological illnesses suffer from conditions for which they seek relief from multiple practitioners in the community. For example, Schwartz and colleagues found that 12% of patients with multiple sclerosis had utilized the services of a chiropractor in the previous 6 months. These patients tended to report fewer emotional problems and express less confidence in their medical health-care plan[22].

Despite the movement towards acceptance of a role in treatment of musculoskeletal conditions, there remains substantial controversy regarding the treatment of other conditions. There are chiropractors who continue to treat patients with a variety of non-musculoskeletal complaints and advertise themselves as providing such services to the general public. This has been a major barrier to integration between chiropractic and main-line health care and has kept it in the realm of alternative medicine, despite the fact that only a small number of chiropractic office visits are for non-musculoskeletal conditions.

At the present time, there are chiropractors practicing in all three capacities—as limited musculoskeletal specialists, as primary providers with musculoskeletal emphasis and as primary alternative health-care providers. In the treatment of spinal disorders and when functioning in inter-professional clinics, chiropractors practice as part of the mainstream healthcare system. Frequently, chiropractors provide treatments that are

complementary to standard health care, sometimes in co-operation with neurologists and other specialists. However, in the treatment of patients with non-muscular conditions for which there is minimal research support, they are best described as practicing alternative health care.

## TREATMENT APPROACHES UTILIZED BY CHIROPRACTORS

Throughout the slightly more than 100 years of the chiropractic profession, the predominant treatment tool has been the 'chiropractic adjustment' or spinal manipulative therapy (SMT). In a retrospective review of office records of 1310 patients who sought chiropractic care for low back pain, 1088 (83%) received spinal manipulation[23]. However, there is significant diversity in the procedures that can be called 'adjustments' or what has been termed SMT. Most of these procedures are properly described as manipulation rather than mobilization. Mobilization employs the passive introduction of forces within the normal passive range of motion of the joint (Figure 1). Manipulation is the term typically applied to movements that are induced at the end of the normal range of motion and that intrude on the 'paraphysiological' range (Figure 1). This is defined as beyond the passive range of motion but less than would be necessary to disrupt spinal integrity. Most manipulative techniques carry the joint to the end of the passive range of motion, with subsequent introduction of a rapid but low-amplitude force to move the joint into this paraphysiological range. These manipulative procedures have been termed high-velocity, low-amplitude (HVLA) manipulations.

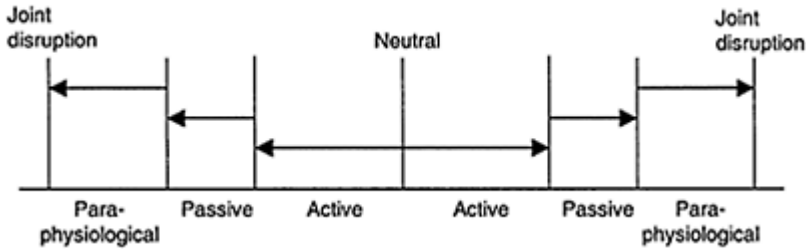


**Figure 1** The active, passive and physiological ranges of motion of a joint

The manipulative force may be introduced directly to one part of the spine, usually using the transverse or spinous process or the spinal lamina as a contact point. Manipulative methods that apply forces to one of the processes of a vertebra are termed 'short-lever' techniques. Examples of lumbar or cervical procedures are shown in Figure 2. Other manipulative procedures direct the primary manipulative force through an arm or leg. These are termed 'long-lever' techniques. The short-lever techniques dominate in chiropractic practice.

There are several other types of procedure employed by chiropractors under the broad rubric of spinal manipulation or adjustment. Some manipulative procedures are initiated

from a neutral position, so-called ‘recoil’ techniques. These are less common than the ‘hold-thrust’ procedures and usually require a special table that permits specific movement of one body part while the remainder of the body is maintained in a fixed position. There are procedures that employ instruments to introduce the adjustive force. The most common of these procedures, called activator technique, utilizes a hand-held, spring-loaded device.

The precise technique used by most chiropractors varies on the basis of the particular area treated. There are literally dozens of short-lever HVLA procedures that have been incorporated into the body of procedures that has been termed ‘diversified technique’. These represent the most commonly practiced chiropractic techniques[15].

Spinal manipulation is not the only form of treatment provided by chiropractors. Contemporary chiropractors incorporate many physi cal modalities such as heat, cold, ultrasound, electrical stimulation and traction[15]. These are usually utilized in conjunction with, and often in preparation for, the spinal adjustment. Many chiropractors advise on therapeutic exercises as a regular part of their treatment regimen and increasingly incorporate full rehabilitation programs. In addition, chiropractors often counsel their patients on nutrition and at times will provide vitamins and supplements as a regular part of their treatment regimen.

## THEORETICAL BASIS FOR MANIPULATION

Early chiropractic theory suggested that misalignments of spinal vertebrae (which was the initial description of what came to be known as subluxation) interfered directly with nerve function through pressure, resulting in changes in physiological processes. These changes were thought to lead to pain and disease[24]. Over the years, however, chiropractic theories have evolved in parallel with the growth in understanding of spinal pathology and spinal mechanics. Today, most chiropractors (and all chiropractic schools) have broadened the original concept to encompass current theories of spinal pathology including concepts of abnormal spinal biomechanics and neurophysiological theories of pain and reflex function[25]. These theories focus on the restoration of joint mobility, relaxation of muscle spasm, modulation of spinal reflexes and the soothing or psychosocial effects of manual therapy.

There is a growing body of experimental studies demonstrating at least short-term effects

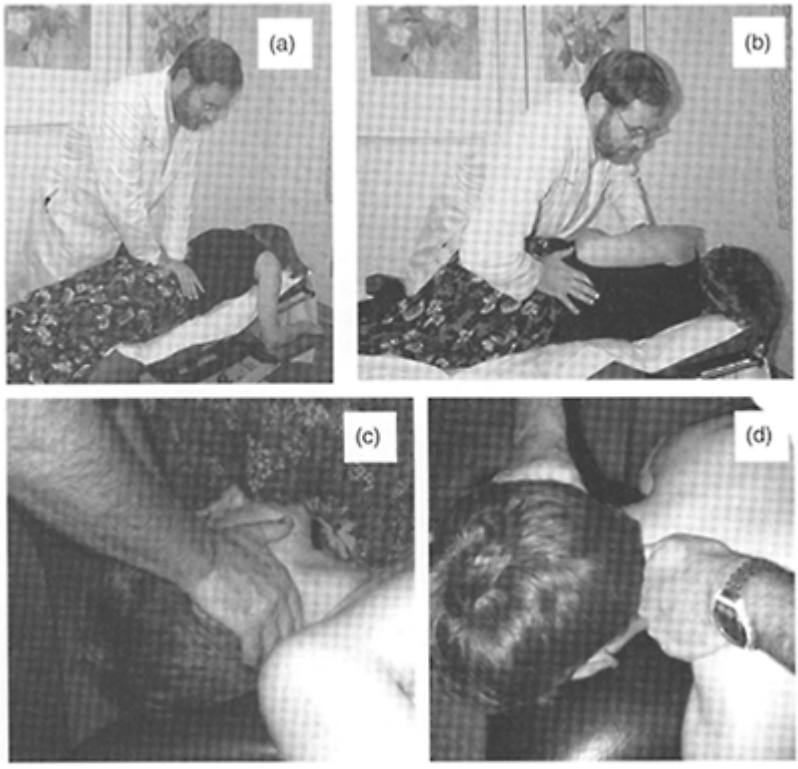


**Figure 2** Several types of chiropractic manipulative procedure. (a) posteroanterior manipulation of the lumbar spine with the patient prone; (b) side-lying manipulation of the lumbar spine with traction placed on the upper thigh and manipulative force by manual contact with the lumbar spine or around the sacroiliac joint; (c) supine cervical manipulation with manipulative contact on the right posterolateral side of the cervical spine and traction with the stabilizing hand; (d) prone cervical manipulation on the left side of the spine

on central processing of pain[26,27]. The most widely accepted theories are based on the theory that immobility of spinal joints is one factor that may lead to joint inflammation, formation of adhesions and degenerative joint disease, and that manipulation may reverse some of these changes[28]. Spinal manipulation is felt to improve joint mobility and restore normal joint function, especially when associated with an exercise and rehabilitation program[29,30].

The most commonly invoked theory on the nature of the subluxation (manipulable lesion) suggests that a vertebral unit can have restricted mobility or be fixated within the normal, physiological range of motion of a joint or may display abnormal motion. Such fixation is proposed to result in pain and abnormal spinal reflex function, including muscle hypertonicity and responses in the autonomic nervous system[31]. Under this construct, SMT is proposed to have a direct effect on muscles and joints and, through receptors in these tissues, an effect on the nervous system. While this theoretical construct is far from proven, there is growing experimental support for it. Magnetic resonance imaging (MRI) studies have indicated a direct effect on spinal joints[32] that is consistent with reports describing increased spinal range of motion following spinal manipulation[28]. Reflex contraction of paraspinal musculature has been demon-strated to accompany spinal manipulation[33]. These observations, however, have not answered the question of the duration of the observed physiological changes or whether these changes are of therapeutic benefit.

Recent neurophysiological research has focused on possible effects of SMT on the central nervous system[31]. Altered pain thresholds have been reported following SMT, possibly related to activation of endogenous pain suppression mechanisms[26]. In addition, abnormal somatosensory evoked potentials from the paraspinal musculature of patients with low back pain have been shown to normalize following manipulation. This suggests a central effect on sensory processing[34,35]. Activationofzygapophyseal joint receptors in rats is capable of markedly attenuating reflex responses in paraspinal muscles to noxious stimulation of nerves in the intervertebral disc, again indicating the interaction between spinal proprioceptors and central pain processing mechanisms[36]. The effect of SMT on the central nervous system has gained further support from the observations by Suter and associates[37], who investigated the effect of manipulation of the sacroiliac joint on the degree of inhibition of quadriceps muscles produced by knee joint pathology. These authors showed that manipulation of the sacroiliac joint decreased this inhibitory effect, suggesting interaction between the manipulation and the inhibition of voluntary activity produced by pain.

Despite many interesting experimental observations, the underlying mechanisms proposed to explain the therapeutic effects of SMT are poorly understood. Considerable further investigation will be required, better to characterize not only the neurophysiology of the spine, but also the processing systems involved in the perception of pain and the patterning of abnormal biomechanical responses to such conditions.

## RESEARCH TRIALS ON CHIROPRACTIC AND MANIPULATION

Detailed discussion of research trials of spinal manipulation is beyond the scope of this chapter and will be deferred to Chapter 15 on alternative approaches to back and neck pain. There are, however, more randomized clinical trials on spinal manipulation for spine symptoms than for virtually any other form of therapy. However, chiropractic treatment is more than spinal manipulation and it is recognized that the more tightly controlled studies of spinal manipulation deviate the most from normal clinical practice. Therefore, there is a body of pragmatic investigation that has compared patients randomized to treatment by chiropractors versus those treated by other methods. Most of these studies have been conducted on back, neck and head pain, the conditions that are most likely to appear in chiropractors' practices.

The success rates reported for manipulation in uncontrolled case series and in comparative trials are between 60 and 100%[38–40]. However, particularly in the case of spinal pain, the general tendency for many patients to improve spontaneously, the problem of different populations of patients and pathological conditions causing pain, coupled with the potentially potent placebo effect of treatment makes it difficult to compare these studies and determine success. Therefore, there has been a growing recognition of the role of randomized comparison trials whenever claims of efficacy are made. Whenever there is no effective placebo group included in a clinical trial, the role of the placebo effect must be considered as a potential mechanism to explain a beneficial outcome. Furthermore, it has been pointed out that designing an appropriate placebo for physical interventions may be particularly difficult[41]. It is in this setting that we will describe the pragmatic studies of chiropractic treatment. The majority of these studies have specifically evaluated outcomes of patients randomized to chiropractic treatment versus those managed by conventional medical means or by physical therapists. Although most studies have considered chiropractic treatment of back pain, neck pain and headache, several studies have evaluated other conditions such as asthma and colic that are beyond the usual realm of what has been considered 'musculoskeletal'.

### Low back pain

The most common reason for seeking chiropractic care is pain in the lower back. Between 30 and 50% of all treatment delivered each year by chiropractors is for low back pain[6,12,42]. Completereview of the 43 trials of spinal manipulation for acute, subacute and chronic low back pain will be deferred for later (Chapter 21). However, several of these studies specifically compare chiropractic treatment to that by other practitioners.

Positive responses for manipulation have been found in patients with subacute low back pain (within 4–12 weeks). In a prospective, randomized trial, Hsieh and associates[43] compared SMT with transcutaneous muscle stimulation, massage therapy or corset use in patients with subacute low back pain. At 3 weeks, the manipulation group showed the greatest improvement in lumbar flexion and in pain scores. Patient confidence was also greatest in the group receiving SMT. There are a limited number of studies that have

examined the effect of chiropractic treatment in patients with chronic low back pain. Waagen and co-workers[44] showed a statistical benefit from manipulation in patients with recurrent or chronic low back pain at the 2-week assessment.

Triano and colleagues[45] compared the use of SMT with a back education program and noted greater improvement in pain and activity tolerance in the manipulation group. Bronfort and co-workers[46] studied the relative efficacy of 5 weeks of chiropractic SMT or non-steroidal anti-inflammatory drug (NSAID) therapy in combination with supervised trunk exercise, followed by an additional 6 weeks of supervised exercise alone. Each of the three therapeutic regimens was associated with similar and clinically important improvement, and there appeared to be a sustained reduction in medication use at the 1-year follow-up period in the SMT and therapeutic strengthening exercise group.

Giles and Muller[47] compared the use of needle acupuncture, NSAID medication and chiropractic spinal manipulation for chronic (i.e. more than 13 weeks' duration) spinal pain syndromes. They randomized 77 patients to these three treatment groups. The main outcome measures were changes (4 weeks vs. initial visit) in the scores of the Oswestry Back Pain Disability Index and three visual analog scales of local pain intensity. After a median intervention period of 30 days, spinal manipulation was the only treatment that achieved statistically significant improvement, with a reduction on the Oswestry scale of 30.7% and reductions on the visual analog scale of 50% for low back pain and 46% for upper back pain. The authors concluded that, in spite of several shortcomings of this study, there was evidence that spinal manipulation resulted in greater improvement than acupuncture and commonly utilized medication in patients with chronic spinal pain.

Meade and colleagues[48] compared a course of nine spinal manipulative treatments performed in private chiropractic offices with six hospital-based physical therapy clinic sessions that included conventional physical therapy as well as some spinal mobilizations. They found significantly greater benefits for the group treated by the chiropractors at several followup intervals: 6 weeks, 6 months, 1 year, 2 years and 3 years. This relative improvement was in terms of both disability and pain. One weakness of the study was the relatively high percentage of patients lost to follow-up, especially at the later time points. Additionally, there were significant differences in treatment settings (i.e. private offices versus hospital clinic). Nonetheless, the large size of this study (enrolling over 700 patients) and the long-term follow-up period with consistent findings over all time points provide some confidence in their findings.

Cherkin and colleagues[49] performed a randomized clinical trial of SMT in a group of 321 patients with low back pain of at least 7 days' duration. They compared SMT with two other treatment protocols, one of which consisted of physical therapy according to the McKenzie method and the other simply the provision of an educational booklet on back pain (termed a 'minimal intervention' group). The group treated by chiropractors performed significantly better than the minimal intervention group at 4 weeks, but not at 12 weeks, 1 year or 2 years. There was no difference between the group undergoing spinal manipulation and the patients treated with physical therapy. Although disability scores were better for both the group treated with manipulation and those patients treated with physical therapy than the minimal intervention, this did not quite reach significance at any time point. It is noteworthy that the groups receiving active treatment were much more satisfied with the treatment, reporting that their care was good or excellent about 75% of the time (compared to 30% of the time for the patients who had been given the

booklet). One limitation of this study was the rather low level of initial symptoms which, when combined with the usual trend to spontaneous improvement of low back pain, resulted in a statistical 'floor effect'. This effect has the potential to limit the ability of a study to detect differences between treatment groups.

These pragmatic studies, combined with the results of other studies of manipulative therapy, argue for some benefit of chiropractic in the treatment of low back pain of various durations versus several other forms of therapy. There is some question as to whether intensive physical therapy may be as effective, at similar overall cost. Additionally, the studies that have been carried out up to the present time cannot determine whether there are particular chiropractic procedures that are more effective than others or whether these treatments are cost-effective. Furthermore, studies have not been designed to address the important question of whether there are particular groups of back pain patients who are more likely to benefit.

### Disc herniation and sciatica

Currently, there are no randomized clinical trials of chiropractic treatment of patients with sciatica and disc herniation. However, there have been a number of case studies and reports that suggest that SMT may be useful for such patients. In a review of data from the back pain clinic at the Royal University Hospital in Saskatoon, the use of side-lying chiropractic SMT (i.e. high-velocity, low-amplitude thrust techniques) was reported to be both safe and effective for the treatment of lumbar disc herniation[50]. In another case series, 71 patients presenting to a chiropractic clinic with low back pain plus sciatica were studied[51]. Ninety per cent[52] of the patients who received a course of treatment reported subjective improvement in both range of motion and nerve root tension signs. These authors concluded that SMT might be a safe, non-surgical treatment for low back and radiating leg pain. Ben-Eliyahu[53], in a prospective study, described good clinical outcomes in 22 (81%) of 27 patients with symptomatic cervical or lumbar disc herniations verified by MRI. Reduction or complete resorption of the disc was seen in 17 patients (63%) in post-treatment MRI scans. However, the lack of a control group makes it impossible to determine whether the improvement could be directly attributed to the manipulation. Despite these promising descriptive case series, it appears that patients with demonstrated disc herniation and sciatica do less well following manipulation than patients with uncomplicated back pain[52].

### Neck pain

Neck pain is the second most common reason that patients seek chiropractic care[6,12,42]. However, substantially fewer clinical trials have been performed on neck pain than on low back pain. Fewer still of these have specifically investigated usual chiropractic care in comparison to other interventions.

Many of the early claims for effectiveness of manipulation for neck pain were based on descriptive clinical studies and large case series. While these reports have been generally enthusiastic, they suffer from a lack of controls and proper research protocols. In addition, the population of patients with neck pain includes a large and heterogeneous group often including patients with headache and other pain symptoms. Different

outcome parameters have been employed in these studies, making it difficult to reach specific conclusions about the efficacy of SMT in the treatment of neck pain. There are a few case reports of patients with cervical disc herniations who have responded to manipulation of the cervical spine[54], but no large controlled trials to support these observations.

Cassidy and associates[28] compared the immediate results of manipulation to mobilization in 150 consecutive out-patients suffering from unilateral neck and trapezius pain. Fiftytwo subjects were treated with cervical manipulation while 48 subjects were randomized to mobilization procedures. There were no significant pretreatment differences between the two groups with respect to history of neck pain or level of disability as measured by the Pain Disability Index. The patients received either rotational manipulation (high-velocity, low-amplitude thrust) or mobilization in the form of muscle energy technique. The results showed that both treatments increased range of motion, but manipulation had a significantly greater effect on pain intensity, with 85% of the manipulated patients and 69% of the mobilized patients reporting pain improvement immediately after treatment. The decrease in pain intensity was more than 1.5 times greater in the manipulated group, leading the authors to conclude that a single manipulation was more effective than mobilization in decreasing pain in patients with mechanical neck pain. There have been two other reports of an increase in cervical rotation and a decrease in neck pain following manipulation when compared with analgesics or no treatment[55,56].

In a randomized, prospective clinical study that included 119 patients with neck pain of longer than 3 months' duration, Jordan and colleagues compared the relative effectiveness of chiropractic treatment to intensive training of the cervical musculature and to a physiotherapy treatment regimen[57]. All three interventions demonstrated meaningful improvement in all parameters, with improvement maintained at both 4- and 12-month follow-up. However, since there was no placebo intervention or non-treatment control group, the authors cautioned that responses may have been due to a placebo effect or simply the passage of time.

Bronfort and colleagues[58] reported the results of a study comparing spinal manipulation alone to either a combination of spinal manipulation and exercise or a high-tech exercise program for the treatment of chronic neck pain. Both of the exercise groups were found to perform better than the group that was treated with only spinal manipulation. However, there was no placebo comparison group or group treated with 'medical management as usual'. This study argues for the incorporation of additional rehabilitation procedures along with spinal manipulation in any program of care, but does not permit the determination of the effect of spinal manipulation independent of other interventions. As described previously, chiropractors typically employ several interventions (potentially including exercise and activity recommendations) in combination with manipulation. From this study, it would appear that such a multimodal therapeutic approach is appropriate.

The previously described study by Giles and Muller[47] also enrolled patients experiencing neck pain. They compared chiropractic SMT with needle acupuncture and NSAID medication, demonstrating that spinal manipulation was the only intervention that achieved statistically significant improvements in neck pain. The authors reported an

improvement of 33% in neck pain on a visual analog scale and 25% in scores on the Neck Disability Index.

The studies on chiropractic treatment of neck pain provide at least preliminary evidence of effectiveness relative to several other interventions. However, it is not at all clear that there is any relative advantage over intensive physical therapeutic approaches. Several additional important studies of spinal manipulation for neck symptoms have provided at least some promising results in this regard. These studies will be discussed in Chapter 15.

## Headaches

Headache is one of the more common reasons for seeking care from practitioners of alterna-tive medicine[3]. It has been estimated that as many as 35% of all patients presenting to a chiropractor have complaints of headaches, often in conjunction with back or neck pain[6,12]. There have been nine published clinical trials of manipulation for various forms of headache, several of which specifically investigated chiropractic treatment in comparison with various other interventions.

Parker and colleagues[59] reported a clinical trial comparing chiropractic treatment with treatment (including mobilization and manipulation) by medical practitioners and physical therapists. This study was small and not of high quality, but it did show improvement in all groups of patients. The group treated by chiropractors was found to report significantly less pain with each headache (while all groups of patients showed similar improvement in frequency of headaches). There was no placebo group or 'no treatment' control group and therefore the natural history and role of placebo could not be determined from this study.

Nelson and colleagues[60] examined the relative efficacy of amitriptyline, spinal manipulation or the combination of both therapies for the prophylaxis of migraine headache. Each group was assigned to 8 weeks of treatment, with the principal outcome time-point being 4 weeks after conclusion of treatment. Clinically important improvements were observed in all three study groups over time. The authors reported that SMT was as effective as amitriptyline. They also noted that there was no advantage to combining amitriptyline with spinal manipulation. It is noteworthy that the effect of manipulation appeared to outlast the treatment period as opposed to the effects of amitriptyline alone. There was no sham treatment group, nor were there patients receiving no treatment. Therefore, the placebo effect and natural history could not be determined from this study.

Tuchin and colleagues[61] reported a study in which 127 patients with migraine were randomized to chiropractic treatment or control treatment with detuned interferential current treatments. There was a 2-month baseline period during which data were collected, a 2month treatment period and a 2-month period during which data were collected regarding headache frequency and severity. The findings showed significantly better outcome in patients who were treated with chiropractic manipulation in terms of frequency and intensity of headache as well as in disability and analgesic medication use. A somewhat surprising finding was that a relatively small fraction of the migraineurs (22%) showed over 90% improvement. However, these authors were unable to identify predictive features for the patients with the best responses.

The results of studies of chiropractic treatment of tension-type headaches are more controversial. Boline and co-workers[62] studied 150 patients with tension-type headaches randomized to chiropractic treatment compared with medical treatment with amitriptyline. There was a 2-week baseline period, 6 weeks of treatment, and the principal outcome measures were evaluated 4 weeks after conclusion of treatment. Both treatment groups improved similarly during the phase of active treatment. At 4 weeks after cessation of treatment, the spinal manipulation group showed a reduction from baseline of 32% in headache intensity, 42% in headache frequency, 30% in over-the-counter medication usage and a 16% improvement in functional health status. By comparison, the group of patients treated with amitriptyline showed no improvement from baseline values. The responses were significantly different between the two groups, indicating a benefit to treatment with manipulation, at least by comparison with a commonly utilized medication.

On the other hand, Bove and Nilsson[63] did not find any significant benefit for chiropractic treatment in patients with episodic tensiontype headache. Specifically, they randomized 26 men and 49 women aged 20–59 years who met the diagnostic criteria for episodic tension-type headache into two groups, one receiving soft tissue therapy and chiropractic SMT, and the other receiving soft tissue therapy and a placebo laser treatment (the control group). Each participant received eight treatments over 4 weeks performed by the same chiropractor. By week 7, each group had experienced significant reductions in mean daily headache hours and mean number of analgesics per day, and these changes were maintained through the observation period of 19 weeks. However, headache pain intensity during the periods of headache was unchanged for the duration of the trial. No significant differences between the manipulation and control groups were observed in any of the three outcome measures.

The reasons for the different conclusions of these two well-constructed clinical trials of chiropractic treatment of tension-type headaches are not clear. However, the study by Boline and associates[62] did not include a control group with any ‘hands-on’ component and this may represent a particularly potent placebo. Based on the divergent results of these studies, additional tightly controlled investigation of chiropractic and tension-type headache would appear to be warranted.

In the case of cervicogenic headache, there has been one clinical trial evaluating the effect of chiropractic treatment in comparison to massage and placebo laser treatment in 53 patients with cervicogenic headache[64]. Both groups were treated for 3 weeks (six treatments) and were evaluated 2 weeks after the conclusion of therapy. The group treated with chiropractic manipulation showed significant benefit in terms of headache intensity, hours per day and analgesic use when compared to the control group.

Summarizing the data on chiropractic and headache, there is good support for the use of chiropractic treatment in patients with cervicogenic headache and, to some extent, in migraine sufferers. There are fewer and conflicting data on therapy by chiropractors for patients with tension-type headaches.

## Carpal tunnel syndrome

While chiropractic manipulation has traditionally focused on spinal disorders, there have been many descriptions of use for problems that affect the extremities. One such condition is carpal tunnel syndrome.

There is one randomized, controlled trial that evaluated the effect of chiropractic in the treatment of carpal tunnel syndrome. This study by Davis and co-workers65 randomized 91 patients with documented carpal tunnel syndrome into two treatment groups, one receiving chiropractic care and the other conventional medical treatment. The chiropractic group received manipulation of the soft tissues and bony joints of the upper extremities and spine (three treatments per week for 2 weeks, two treatments per week for 3 weeks and one treatment per week for 4 weeks), ultrasound over the carpal tunnel and nocturnal wrist supports. Those in the medical treatment group received ibuprofen (800 mg three times a day for 1 week, 800 mg twice a day for 1 week and 800 mg as needed to a maximum daily dose of 2400 mg for 7 weeks) as well as nocturnal wrist supports. Outcome measures included pre-and post-assessments of self-reported physical and mental distress, nerve conduction studies and vibrometry. There was significant improvement in both groups in terms of perceived comfort and function, nerve conduction values and finger sensation. However, these investigators found no significant differences between the groups. Since there was no control, it is again not clear whether either intervention was better than doing nothing. It is noteworthy that the manipulation group offered significant advantage in terms of complications, with 22% of those receiving ibuprofen reporting some intolerance and 11% reporting severe side-effects requiring discontinuation of the medication. In contrast, only one patient in the chiropractic group complained of a temporary sore neck because of the manipulation. This would at least suggest that chiropractic treatment is a viable alternative for management of carpal tunnelrelated symptoms.

## Other disorders

Although the vast majority of patients are seen by chiropractors for musculoskeletal symptoms, the chiropractic literature is replete with descriptions of effective treatment of various internal and neurological disorders. While many of these appeared in books over the first half of the 1900s, and notwithstanding that many of these probably represented misdiagnoses in the first place, more recent literature includes reference to treatment of conditions as diverse as myasthenia gravis[66], epilepsy[67], Parkinson's disease[68], reflex sympathetic dystrophy[69], torticollis[70], cervical dystonia , fibromyalgia and Erb's palsy without adequate explanation. Case reports, even if taken at face value, do not control for spontaneous fluctuations in symptoms or potentially powerful effects of expectation on the part of patients. It is this type of anecdotal case report that reinforces the skepticism amongst medical practitioners on the motives and claims of chiropractors. It should be noted, however, that not all of these claims for manipulative effects have been made by chiropractors. A significant fraction appears in the peer-reviewed osteopathic literature and European medical literature as well, potentially lending greater credence. However, it

is clear that all such observations require validation and that 'extraordinary claims require extraordinary proofs'.

Lately, there has been a move to investigate some of these claims. As described previously, asthma is among the most frequent non-musculoskeletal complaints treated by chiropractors. Chiropractic treatment of asthma has been investigated in two randomized clinical trials, which failed to find any objective benefit of manipulation in comparison to treatment as usual[74,75], althoughpatients treatedbychiropractors rated their symptoms after treatment as being less severe, and their quality of life as improved. A systematic review of the literature concluded that there was insufficient evidence to support the use of manual therapies for patients with asthma, while there was a need for additional studies on the subject[76].

Another observation that has been the subject of rigorous scrutiny is the potential effectiveness of chiropractic treatment of infantile colic. Two randomized controlled trials have been conducted, both of comparable design and of good quality[77,78]. The two major differences between these studies were in the degree of blinding of parents who completed the crying diary and in the treatments that were permitted. In one trial[78], parents were blinded as to the assigned treatment group, adding credence to their conclusion that chiropractic offers no greater efficacy in treating infantile colic than placebo. However, these investigators restricted the chiropractic treatments to three manipulative sessions in the span of 8 days, which most chiropractors would regard as an inadequate trial. On the other hand, the positive effects of spinal manipulation reported in the second study[77] were dramatized by the fact that they had nine dropouts from the study, all in the medication treatment (dimethicone) group and all as a result of a worsening of symptoms. There were no dropouts from the chiropractic group. At the present time, it would appear that there is a clear indication for more study of this issue, a subject that might well have been rejected out of hand had there not been some initial suggestion of benefit.

## COST EFFECTIVENESS AND PATIENT SATISFACTION

Cost has become an increasingly important outcome measure. To date, there have been approximately 20 studies that have looked at the relative costs of chiropractic treatment in patients receiving workers' compensation. Fourteen of these studies demonstrated a lower cost compared to traditional care[79–82]. In 1989, Johnson and colleagues[80] demonstrated that the mean disability compensation paid to workers with back and neck injury was $264 for those treated by chiropractors compared to $618 for those treated by medical physicians. In a 1991 report, Jarvis and co-workers[81] compared treatment costs for identical diagnoses and noted the treatment cost to be $527 for chiropractors and $684 for physicians. In a review of workers' compensation studies through 1993, Assendelft and Bouter[83] concluded that, although the majority of studies up until that time had demonstrated some relative cost benefit for chiropractic, methodological concerns prevented definitive statements and this remains an open question to the present time.

Differences between chiropractic and medical costs are less evident in the private insurance arena and depend on the treatment to which chiropractic is being compared. The study by Carey and co-workers in 1995 suggested that the cost of chiropractic care

was similar to the cost of orthopedic care and more than the cost of care by an HMO family practice physician[84]. The slightly lower cost of care for back pain episodes treated by primary care physicians versus chiropractors has been observed to hold true even in studies reported as recently as 2002[85]. This does not appear to hold true when comparing all sufferers from back pain who initially consult chiropractors versus medical physicians, potentially owing to a bias for particularly high-cost care (both diagnostic and therapeutic) on the part of some medical providers[81]. Non-randomization of patients in these studies leads to concerns about whether patients are similar or not between the two groups of providers.

Cherkin and colleagues[49] addressed this question by evaluating cost and effectiveness in a randomized sample of 321 patients enrolled in an HMO who had experienced low back pain for at least 7 days. The three treatment approaches included chiropractic treatment, physical therapy and a minimal intervention group (an educational booklet on back pain). It is noteworthy that this study included a wide range of acute and chronic patients. In terms of effectiveness, the group treated by chiropractors performed significantly better than the minimal intervention group at four weeks, but not at 12 weeks, 1 year or 2 years. However, there were no differences between the group treated by chiropractors and those patients treated by physical therapists either in terms of outcome or cost. Not surprisingly, both of the active treatment groups cost more than the group only given the booklet. Disability scores were better for both the manipulation and the physical therapy patients than the group given the booklet. However, this did not quite reach significance at any time point. As described previously, the low levels of initial symptoms in the study may have limited the ability to detect a difference and both of the groups receiving active treatment were much more satisfied with treatment than those given the booklet. It is also important to note that neither of these insurance industry studies included consideration of the costs of disability in their cost analysis.

Skargren and colleagues[86,87] comparedcost and effectiveness of treatment of chronic back and neck disorders by chiropractors versus treatment by physical therapists. These authors found no difference between the two groups in terms of health improvement, costs, or recurrence rate. The chiropractic group fared slightly better (pain and disability) if the current episode was of less than 1 week, while physiotherapy was better if the episode had lasted longer than a month. There were no significant overall differences between the two treatment groups at 6 months[86] or 1 year[87]. Unfortunately, the authors did not evaluate data from the patients with neck pain independently from those with back pain, so specific conclusions cannot be drawn relative to cost or effectiveness for individual complaints.

Both the study by Carey and colleagues[84] and that by Cherkin and colleagues[49] showed significantly higher satisfaction amongst patients treated with spinal manipulation than in patients receiving comparative treatments. Other studies that have looked at the degree of satisfaction in patients seeking manipulative therapy or chiropractic care have reached a similar conclusion, demonstrating much higher patient satisfaction scores compared to other forms of treatment, including conventional medical care. The difference is not as great when manipulation is compared to massage[88]. This may be due to the time spent by chiropractors with a patient, the simple laying on of hands, the personal attention offered patients by most chiropractors or the frequency of visits, which tend to be higher than for other treatments. The study by Pope and

colleagues demonstrated increased satisfaction the longer the care continued, which suggested that personal contact with the practitioner may be the overriding factor[88].

## COMPLICATIONS OF MANIPULATION

Spinal manipulation, like all forms of treatment, can have side-effects. Nearly half of all patients who undergo spinal manipulation experience side-effects such as local discomfort, headache, or tiredness[89,90]. Fifteenper cent of these side-effects were described as 'severe' in intensity, but these symptoms usually disappeared within 24 h. The magnitude of the more serious complication risk has been difficult to assess. Up to the present, no serious complication has been reported in any of the controlled clinical trials or in any prospectively evaluated case series.

The perceived risk of cerebrovascular injury following cervical manipulation has been a particular source of concern. The risk of vertebral artery dissection has been estimated by various authors using different methodology to range from 1 in 400000[91] to between 3 and 6 per 10 million manipulations. These figures have been primarily based on retrospectively collected single case reports and case series[92,93], and practitioner surveys[91,94]. There has been one retrospective cohort study that examined the incidence of cerebrovascular accidents after manipulation[89]. It covered the period 1978–88, and the experience of 99% of the practicing chiropractors in Denmark. Over 10 years, five arterial dissection cases and one fatality were identified, representing approximately one serious complication for every 1 million cervical manipulations. The only case-control study published to date on this topic is that by Rothwell and associates[95]. They concluded that no temporal relationship existed between spinal manipulation and stroke for patients over the age of 45 years. Under the age of 45 years there was a five-fold increased likelihood that a patient would have visited a chiropractor in the past week or received three or more treatments within the past month before the vertebral artery occlusion or dissection, when compared to controls. A positive association was noted between cervical manipulation and vertebrobasilar artery stroke in 1.3 cases in every 100000 patients receiving chiropractic care. Assuming that patients are likely to receive 8–14 chiropractic treatments during the course of care[6], this number approaches the one in 500000 to 1 million manipulations noted from the various surveys. It is important to note that in only nine cases out of 582 with vertebrobasilar arterial strokes in the province of Ontario could any temporal association be found between chiropractic treatment and stroke. Furthermore, the results of this study yielded the statistical anomaly that the odds ratio for stroke was actually significantly less than in controls for patients who received manipulation 8–30 days before the stroke. Finally, this study also did not consider the potential confounding effect of patients seeking chiropractic treatment for acute neck pain associated with an evolving dissection of the vertebral artery. All of these issues will require detailed, prospective investigation if true understanding of risk is to be determined.

The RAND study estimated the rates of serious complications as 5–10 in 10 million for vertebrobasilar reactions, 3–6 in 10 million for major impairment, fewer than three fatalities per 10 million manipulations, and about 1 per 100 million complications involving cauda equina following lumbar manipulation[96]. If these numbers hold up to

further scrutiny, spinal manipulation would be among the safest treatments available for spinal disorders.

## SUMMARY

Since the end of the 19th century, chiropractic has moved from a profession that was ostracized and marginalized to a position where integration into the mainstream health-care system is not only possible, but is actually in process. This has been largely due to the development of a defined and regulated chiropractic educational process, licensure, insurance recognition and a growing body of clinical research that supports the use of chiropractic treatment for some conditions. These privileges have come about primarily through a strong public demand for chiropractic and a commitment on the part of chiropractic academic institutions to outcomesbased research to evaluate clinical claims.

The exact role of chiropractors in the treatment of disorders outside the classic realm of the musculoskeletal system, however, remains controversial. Although there is a reasonable body of controlled clinical research to support a role for chiropractors in the treatment of low back pain, neck pain and certain types of headache, it is not yet easy to identify the patient most likely to respond to manipulative treatment. The exact mechanism by which manipulation obtains its success is not well understood, although this is an arena of increased study. The issue of claims for effectiveness based on anecdotal experience and case reports remains a source of contention between chiropractors and medical practitioners. These issues are slowly being addressed and it can be expected that the future will bring greater clarity in our understanding of the role of chiropractic, if any, in the care of patients with disorders beyond the musculoskeletal system. It can be anticipated that patients will continue to seek the care of chiropractors in ever-greater numbers. Improvement in understanding of the role of chiropractors and other alternative and complementary practices should therefore be considered to be in the best interest of the significant fraction of patients who combine these treatments with more conventional medical care.

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# 4
# Osteopathic considerations in neurology

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*Complementary Therapies in Neurology: An Evidence-Based Approach*
Edited by Barry S.Oken
ISBN 1-84214-200-3 

## INTRODUCTION AND HISTORY

The osteopathic profession in the USA consists of approximately 50000 physicians, with more than 60% of the profession made up of primary care practitioners. With the number of osteopathic colleges quadrupling to 20 since 1969, it is the fastest growing health profession in the USA. Osteopathic practitioners (DOs) include specialists in every specialty field practiced by allopathic physicians (MDs) in the USA, but maintain their own educational system based upon four tenets; for this reason it has been referred to as a 'parallel but distinctive' profession[1].

Osteopathic medicine has been described as an integration of science, philosophy and art[2]. It is defined as 'a complete system of medical care with a philosophy that combines the needs of the patients with the current practice of medicine, surgery, and obstetrics; that emphasizes the interrelationship between structure and function; and that has an appreciation of the body's ability to heal itself'[3]. Such emphasis on structure (anatomy) and function (physiology) naturally increases the emphasis on the central role of the neuromusculoskeletal system. Indeed, the early development of osteopathic medical concepts emphasized the role of the nervous system as an integrator of function between the various systems of the body[4], especially the soma and the viscera.

Regardless of their eventual specialty field, all of the profession's caregivers spend a comparatively heavy amount of their pre-doctoral training in the study of anatomy—especially the structure and function of the somatic system (skeletal, arthrodial and myofascial components) and their functional interrelationships to neural, vascular and lymphatic structures—and neurophysiology (especially the autonomic nervous system). In addition to the more traditional neurology and neurosurgery specialties, the osteopathic profession includes an additional residency program and specialty known as neuromusculoskeletal medicine (until 1998 referred to as osteopathic manipulative medicine, OMM).

While osteopathic medicine and surgery are recognized as mainstream practices throughout all 50 of the United States, the profession is perhaps most distinctive in its educational approach and in its expectation that, prior to graduation, its eventual practitioners are all required to study and demonstrate safety and efficacy in applying

osteopathic principles and practices (OPP) and osteopathic manipulative treatment (OMT). Testing involves written and practical examinations within the individual schools as well as through all three levels of the national board examinations administered by the National Board of Osteopathic Medical Examiners. Some osteopathic specialty boards (including osteopathic family medicine—the largest board) conduct a hands-on practical examination of OMT. Also, a number of states require additional demonstration of safety and efficacy in OMT before granting a license to practice as a physician or surgeon in that state.

By the definition of the National Institutes of Health (NIH) National Center for Complementary and Alternative Medicine (NCCAM), the same OMT that is taught and required to be mastered by all DOs in the USA is, in isolation, categorized by them as being a 'complementary and alternative' therapy. For this reason this text includes a chapter on osteopathic medicine but will not attempt to describe all facets of the profession.

This chapter provides a brief overview of the impact that OPP and OMT have made in the profession's history and why there was a general lack of acceptance of the profession by the traditional medical profession until the 1960s and 1970s. It also comments on the evolution of OMT as a treatment modality and mentions techniques that are commonly used. It focuses on some of the contributions that the osteopathic profession has made to health care generally by maintaining a distinctive philosophy and modality. Finally, this chapter discusses the rationale and outcomes of applying an osteopathic approach that includes OMT as part of the care for patients with varying neurological conditions.

## History of osteopathy

Osteopathy began in rural Kirksville, Missouri. It was developed and named by a traditional physician, Andrew Taylor Still, MD. Disillusioned when drugs failed to save the lives of several immediate family members during a spinal meningitis epidemic and when a brother became addicted to morphine, Still re-examined the orthodox medicine of his day, found it wanting and began a pathway of study of somatic structure and function. He came to believe that the body contained all substances needed for health, that 'perfect anatomy' should lead to removal of waste products and that the delivery of nourishing blood and trophic substances improved health at the cellular level. He believed that structural impairment would restrict this process, initiating instead the progressive processes of dysfunction, 'dis-ease' and eventual disease.

During the period in which osteopathy developed, Still was not alone in his pursuit of an alternative to 'mainstream' or 'regular' medicine. Regular medical practice was generally criticized both professionally (Oliver Wendell Holmes) and popularly (Mark Twain—also from Missouri and an osteopathic advocate). The public was initially impressed by a number of the alternative medical practitioners of the day, then called 'irregulars'. Still investigated several of their therapies—including 'magnetic healing' and 'lightening bone-setting'—practices that some say influenced his thinking and techniques. Others suggest that scientific treatises discussing the somatic treatment of 'spinal irritation'[5,6] mayhaveinfluenced his integration of a manual approach to the spine in treatment of individuals with a wide range of illnesses.

Whatever his influences, Still wrote that his original thoughts were clearly identified in 1874[7]. His insistence on incorporating handson treatment was considered 'blasphemous' and prevented him from opening a school to teach his approach in Baldwin, Kansas at a university that his family helped to found. He was subsequently ejected from the Methodist church on the basis that only Christ was allowed to heal by the 'laying on of hands'[8]. When he opened the American School of Osteopathy (ASO) in Kirksville in 1892, the stated goal of the school was 'to improve our present system of surgery, obstetrics, and treatment of diseases generally, and (to) place the same on a more rational and scientific basis, and to impart information to the medical profession'[9].

In 1889 he had named his new approach 'osteopathy' from the roots *osteon*, meaning bone, and *pathos*, meaning to suffer. He selected this name because it denoted the bony skeleton that had served as his 'starting point' for understanding clinical problems and it paralleled other medical system names of that period, including allopathy and homeopathy. While the name seems to imply a unifocal fixation on bone, Still taught that 'the fascia is the place to look for the cause of disease and to begin the action of the remedy' and that 'the rule of the artery was supreme'. Bones were available for 'use as levers to relieve pressure on nerves, veins and arteries'[7]. Manipulative procedures were designed to release bony and soft tissue barriers affecting nervous and circulatory functions with the expectation that the body's self-healing (homeostatic) mechanisms would then return the person to health. He taught that 'Rational methods of treatment are based upon an attempt to provide normal nutrition, innervation and drainage to all tissues of the body, and these depend chiefly upon the maintenance of normal structural relationships'[10].

Throughout Still's lifetime and thereafter, the osteopathic profession did not consider OMT to be an isolated treatment modality. From the beginning, the ASO and its infirmary promoted the use of antiseptics and anesthetics in surgery and antidotes to poisons. Still continued to practice and teach obstetrics. The centrality of OMT in the curriculum—even to the potential exclusion of teaching pharmaceuticals—was frequently debated, but the osteopathic teaching institutions decided to prepare their graduates for complete licensure regardless of Still's personal thoughts about the *Materia Medica.*

Within two decades, osteopathic medicine in the USA moved from a single practitioner to ten colleges with practitioners located in the majority of the United States and in several international sites. It escaped the trap of many other alternative medical approaches that became virtual cults by revering their founders' words to the detriment of the integration of new discoveries and approaches. One hundred years later, a conclusion by both MD and DO leaders in the Macy Foundation Report[13] was that the USA benefits from the parallel but distinct medical systems. It is predicted on the potential of each to contribute uniquely and synergistically to health care.

## History of research in osteopathic palpatory diagnosis and osteopathic manipulative treatment

From almost the beginning of the profession, researchers at the ASO in Kirksville investigated what was called the 'osteopathic lesion'. In 1898, researchers used skiagraphy, an early form of X-ray, to look at alignment of bones and distribution of the vascular and lymphatic systems[14].

Profession-wide funding for the A.T. Still Research Institute beginning in 1906 with Louisa Burns, DO as the director, resulted in nearly four decades of publication [15–17]. Her research at the institute focused on the effect of extrinsically induced somatic dysfunction in a rabbit model. The results indicated that straining specific vertebral segments produced reproducible constellations of change in organs and tissues sharing the same segmental innervation as the area of strain. Wilbur Cole, using various neural stains, later substantiated many of these changes[18].

From 1945 to 1970, human measurements and further inquiry into the basic mechanisms underlying somatic dysfunction were undertaken in Kirksville by a team of osteopathic physicians and PhD physiologists[19–22]. Both the palpatory characteristics and the physiological impact of segmental spinal somatic dysfunction were documented with a variety of emerging neurophysiological tests including electromyography. Somatic dysfunction (called the 'osteopathic lesion' until the 1960s) was demonstrated to be an objective finding with reproducible and predictable effects on neurophysiological parameters. The results from studies of muscle reactivity, sweat gland and electrical skin resistance changes, and histamine responses (among others) contributed to the physiological concept of a facilitated spinal cord segment—generally an expansion of the concept of neural facilitation. Yet other studies from the Kirksville team led to a better understanding of axoplasmic and reverse axoplasmic flow[23]. In short, the research of this laboratory resulted in a conceptual framework that has supported much of today's thought concerning palpatory diagnosis and use of OMT to modify neurophysiological function[24–27].

Since 1970, the rapid expansion of university-based and/or state-sponsored osteopathic colleges as well as the acceptance of US-trained osteopathic physicians as medical colleagues with valuable information to offer about manual medicine has led to a series of national and international congresses concerning the evidence base of manual medicine including OMT[28–31] The diagnosis and definition of 'somatic dysfunction', as proposed by the osteopathic profession, was accepted into the *Hospital Adaptation of the International Classification of Disease*. During this period, DOs from the USA were allowed representation in the physicians-only International Federation of Manual/Musculoskeletal Medicine with subsequent rich exchange of professional information, advancing the evidence base and treatment options in this field.

By systematically studying somatic dysfunction and its effects, the osteopathic profession has contributed greatly to the literature and therefore to the understanding of a wide range of health-care professionals who assess the function of the neuromusculoskeletal system. Likewise, it has benefited from the basic science contributions of other professions studying chiropractic subluxations, myofascial trigger points, or other 'impaired or altered functions' of components of the neuromusculoskeletal system.

The wide range of osteopathic manual techniques designed to treat somatic dysfunction has largely been adopted by the bulk of those health-care professionals currently delivering hands-on care. Inter-professional collegiality also permitted the osteopathic profession to integrate studies of manual techniques from others. In this arena, for 'technique' or fixed 'technique protocol' studies, the degree of the researcher or 'technician' delivering the technique is less important than their documented skill to do so in a consistent manner to obtain a certain specified goal.

Looking ahead, however, the osteopathic profession needs to move beyond adding a technique or technique protocol to conservative care and towards completing larger outcome studies and studies of the cost-efficacy of the 'osteopathic approach'. Statewide analysis of Workers' Compensation data[32–34] by different health-care practitioners, including physical therapists, chiropractors, MDs and DOs, revealed that, in every body region and in every condition, the osteopathic practitioners were the most cost-effective with their approach. The data, however, did not indicate where palpatory diagnosis might have been used to exclude the need for a more expensive radiological study; where manipulation might have facilitated recovery and decreased the time absent from work; or, for that matter, when OMT had been a treatment modality and when it had not. In other words, these data cannot be used to prove the cost-efficacy of OMT but raise some interesting considerations regarding the importance of the application of osteopathic thinking and treatment modalities for the care of patients with injuries, dysfunctions or disease.

That OMT is capable of altering or eliminating somatic dysfunction is not contested; nor that somatic dysfunction treated with OMT (or other clinical approaches) leads to beneficial change in a number of physiological and neurological parameters. Nonetheless, until recently, the evidence that OMT affects significant clinical outcomes for given conditions has been largely anecdotal.

Today, osteopathic schools are the recipients of research grants from the NIH and other sources. While such research contributes significant new knowledge in a wide range of clinical and basic science fields, only a small percentage of the total research output of the osteopathic profession today is focused on expanding the evidence base for somatic dysfunction and manipulative techniques, or for the osteopathic approach to patients with specific medical, traumatic, obstetric, or surgical conditions. By virtue of the nature of the questions asked and the research design required, it has been particularly difficult to obtain sufficient research dollars to construct longitudinal studies in OMM.

## Accessing and building upon osteopathic research

While the osteopathic profession has embraced research since its inception, it has been primarily recognized for its clinical service (especially in primary care) rather than for its research contributions. This is partially due to the fact that the profession's research contributions in this area are difficult to locate and also because its research conclusions translate poorly into clinically relevant practice.

A brief historical comment is pertinent to understanding part of the difficulty in accessing large portions of the evidence base for OMT. Prior to 1970, the policy of the American Medical Association (AMA) was to consider interactions between MDs and DOs as 'unethical,' thus osteopathic research was, by necessity, published within the profession's own journals (such as the *Journal of the American Osteopathic Association* and *Osteopathic Annals*) and the American Academy of Osteopathy's yearbooks. In 1966, AMA policy changed and the *Journal of the American Osteopathic Association* was accepted as an *Index Medicus*-referenced, peer-reviewed journal. The profession also was slow to develop and publish a standardized *Glossary of Osteopathic Terminology* to provide language, a thesaurus for indexing its literature, and the resources and personnel to accomplish these tasks. This glossary was first published in 1981. In the mid-1990s,

the American Osteopathic Association (AOA) Bureau of Research and the American Association of Colleges of Osteopathic Medicine authorized finances needed to catalog the older osteopathic landmark research and the earlier basic studies and to place these into a database allowing computerized literature searches. (The current site for search is http://ostmed.hsc.unt.edu/).

It is understood that the research designs required for drug trials are not ideally suited to the study of many of the pertinent questions raised by the osteopathic approach. The randomized, double-blind research 'gold-standard' is often difficult to apply to the study of the osteopathic approach because of the profession's philosophical emphasis on health rather than disease and its prioritization of individual host factors in constructing a therapeutic prescription. Blinding, with respect to manual techniques generally, has been problematic and consensus on an adequate 'sham treatment' for such manual approaches has not been reached.

It is sometimes difficult to decide which OMT protocol or even which specific manipulative technique should be tested for patients with a certain dysfunction, injury, or disease. This is because OMT is typically not applied in such a way in practice. OMT, as practiced by osteopathic physicians, is generally not prescribed for the disease *per se*, but is instead selected and modified for the concomitant somatic dysfunction that is produced and found in each patient reacting to the disease. Thus, in real life, OMT sequences and technique choices are directed by continuous interpersonal feedback between patient and physician as well as by the local, regional and systemic response of the patient to the previous technique selected and delivered. Each patient responds differently. To write an OMT protocol, in advance, for a series of very different individuals having only a specific disease process in common is likely to miss the inherent questions that the profession would like to have answered.

## DIFFERENTIATING OSTEOPATHIC MANIPULATIVE TREATMENT FROM OTHER MANUAL TECHNIQUES

Still observed that 'Not all manipulators are osteopaths'. This is particularly true today, as many health-care professionals incorporate hands-on manual maneuvers. Outnumbering DOs and possessing fewer overall therapeutic options, most manipulation in the USA is performed by members of the chiropractic profession. Founded several years after the osteopathic profession and only a few hundred miles from the birthplace of osteopathy, chiropractic was able to grow as a separate profession by virtue of the fact that there were wide differences in both the types of manual technique employed and the philosophical differences in practitioners' decisions as to how, when, why and where to manipulate[35]. Significant differences still exist between the two professions in both diagnosis and the manipulative techniques that are employed, yet, as the evidence base increases, internationally and across all professions, these aspects are independently evolving in similar directions. Today, by virtue of education and license, the greatest difference between the chiropractic and osteopathic practitioners can be found in the training and the unlimited range of therapeutic options that are available to osteopathic physicians.

On the other hand, OMT is often reported to be the most outward and visible sign of the difference between MDs and DOs. Nonetheless, the modality of OMT alone does not differentiate the two professions. It should be pointed out that many DOs choose not to integrate OMT into their practices and many MDs learn manual techniques in postgraduate coursework and integrate these into their practices.

Neither is a manual modality appropriately termed 'OMT' just because it was delivered by a physician with a DO degree. OMT, by definition, is 'the therapeutic application of manually guided forces…to improve physiologic function and/or support homeostasis that have been altered by somatic dysfunction'[36].

OMM denotes the 'application of osteopathic philosophy, structural diagnosis, and the use of OMT in the diagnosis and management of the patient'[36]. The importance of the integration of osteopathic philosophy and the OMM perspective cannot be overestimated in understanding the distinctiveness of the osteopathic profession. Just as the philosophical underpinnings of the acupuncturist differentiate needling from acupuncture, so the osteopathic perspective of philosophy, science and art modifies the choice and site of the application of a given manual technique and differentiates OMT from a chiropractic adjustment or an MD-applied manual medicine maneuver. Thus, for those critically evaluating clinical outcomes, for those referring patients for osteopathic care and also for the patient, the difference in the semantics is important.

It is probably for this reason that MDs currently practicing in the field of 'manual medicine' recognize that there is a difference between those who add manipulative/manual techniques to a medical practice and those physicians who have distinctive osteopathic training and are therefore practicing OMT as an 'osteopathic' manipulative treatment.

In summary, OMT played a central role in the history of the osteopathic profession and was a central component in discussions sponsored by the Macy Foundation. Leaders noted the specific need for expanding the evidence base and in demonstrating the mechanisms of action and clinical outcomes associated with OMT. Regarding osteopathic clinical practice, the Macy conference chairperson, D.Kay Clawson, noted, 'There are some of us in the allopathic world who believe sincerely that osteopaths have something very special in their practice that needs to be highlighted by all of us.'[13] Of OMT specifically, one keynote presenter from the Association of American Medical Colleges presented the conclusion: 'And if, (the osteopathic) belief that this approach to patient diagnosis and therapy proves to be valid, then I think all physicians ought to utilize it to improve the quality of the health care that we deliver.'[37]

## Palpatory diagnosis and osteopathic manipulative modalities

Dr Still's teaching emphasized anatomy and not the specifics of his hands-on technique. Today, however, the curriculum of osteopathic colleges includes several hundred hours reserved for specifically teaching the art of palpatory diagnosis and manipulative technique and for testing the cognitive, psychomotor and affective aspects of OMT and OMM. There are over 50 different types of technique taught for treatment of somatic dysfunction in every region of the body and for its effect on homeostatic functions in patients with diverse medical, surgical and other health problems[38]. (See Table 1 for some of the more commonly used techniques[3,39].) Many of these techniques have been

adapted or adopted into the armamentaria of other professions—chiropractors, physical therapists and manual medicine physicians.

Most of these techniques have a long and respected tradition with clinically significant outcomes in the literature supported by practitioners of various types. Other techniques have little research support beyond the inherent logic of improving structure-function relationships or homeostatic mechanisms. Most have long histories of empirical evidence and postulated mechanisms that have scientific support ranging from preliminary to conclusive.

While OMT technique is specifically taught and tested at all American osteopathic colleges, the original Still admonition remains somewhat the same; osteopathic students are often reminded that 'The technique used is usually less important than the clinical goal.'[2] That said, the technique to achieve the goal must be carefully chosen. In discussing the 'osteopathic prescription'[40], Paul Kimberly, DO, notes the importance of matching physician skills in delivering the technique with patient host factors that may indicate a relative contraindication to a particular technique.

In designing an osteopathic prescription, the physician weighs the risk/benefit ratio for the use of OMT. If indicated, he or she selects from a number of techniques using direct, indirect, or combined methods and a variety of activating forces (see Table 1) to accomplish specific clinical goals. Like choosing a medication, each has a spectrum of action and relative contraindications. For example, certain direct method techniques might be avoided in the hypermobile patient or in an area with suspected osteoporosis or cancer. 'Dosage' and 'frequency' of treatment are usually determined by the patient's response to the OMT that was selected and provided after careful evaluation. A flare-up of an underlying rheumatological condition or of the presenting

**Table 1** Commonly used osteopathic manipulative treatment (OMT) techniques

| |
|---|
| *Direct method techniques to treat somatic dysfunction* |
| High-velocity, low-amplitude—thrust |
| Low-velocity, moderate-amplitude—springing |
| Low-velocity, high-amplitude—articulatory/ range of motion |
| Direct myofascial release Percussion vibrator |
| Spencer technique (shoulder) |
| V-spread for cranial sutures |
| Progressive inhibition of neuromuscular structures |
| Soft-tissue OMT |
| Stretching |
| Kneading |
| Deep friction |
| Tapotement |
| Petrissage |
| Muscle energy (isometric) |
| *Indirect method techniques to treat somatic dysfunction* |

Functional
Exaggeration
Balanced ligamentous tension
Indirect myofascial release
Counterstrain
Facilitated positional release
Indirect balanced membranous tension

*Combined method techniques to treat somatic dysfunction*

Still technique
Integrated neuromuscular release
Fascial unwinding

*'Homeostatic' treatment techniques to enhance health*

Galbreath mandibular drainage technique for
Eustachian tube
Splenic pump for immune function
Collateral ganglion inhibition
Visceral OMT (ventral technique)
Mesenteric lift
Lymphatic pumps

Dalrymple pedal pump
Classic thoracic lymphatic pump

CV 4

Rib raising

patient complaint—particularly if it lasts more than 24 h—often warrants re-evaluation of the manipulative prescription including the choice of techniques, activating forces employed, amount of treatment rendered and, perhaps, even the role of using OMT as a primary or adjunctive treatment procedure.

Goals for OMT center on removing the diagnosis of 'somatic dysfunction', reducing pain/nociception, enhancing postural muscle balance or balance between agonist-antagonist groups; and/or enhancing a given homeostatic mechanism. Each of these goals is discussed below from its neurological perspective in relation to somatic dysfunction.

## SOMATIC DYSFUNCTION: A NEUROLOGIC PERSPECTIVE

Somatic dysfunction is defined as 'impaired or altered function of related components of the somatic (body framework) system: skeletal, arthrodial, and myofascial structures, and related vascular, lymphatic, and *neural elements*. Somatic dysfunction is treatable using OMT[36]. The italic print in the previous definition was added to emphasize the fact that neural elements are an integral component in osteopathic diagnosis and treatment. Also note that, by definition, somatic dysfunction is responsive to OMT, i.e. it can be removed. This differentiates it from other pathological processes (such as osteoarthritis or fracture,

for example) that might also impair somatic functions and have effects on related elements.

Somatic dysfunction is a codeable diagnosis in the *International Classification of Disease.* Four objective components make up the diagnosis: tenderness, asymmetry, restricted motion and tissue texture change. These four components are known by the mnemonic, T-A-R-T. These components have been examined for both articular and myofascial somatic dysfunctions and studies indicate acceptable inter-examiner reliabilities[41–44]. Asingle OMT technique may reduce or eliminate all or part of the T-A-R-T constellation in a given somatic dysfunction.

Recent advances in the basic sciences suggest that the clinical phenomenon of somatic dysfunction that is addressed daily by practitioners using OMT or other manual, pharmacological, or physical medicine approaches, is in fact multifactorial. It must therefore be recognized that elucidating a single cause for somatic dysfunction or a single pathway for explaining the effect of manual techniques is not feasible, especially in a review chapter. Nonetheless, there is merit in examining some of the more enduring models for somatic dysfunction to gain better understanding of the clinical goals for and expectations from OMT.

Early research on the neurologic underpinnings of somatic dysfunction by PhD and DO investigators, demonstrated distinctive differences in various tissues as well as both somatic and autonomic responses to various stimuli[22,45]. Subsequent independent research by PhD and MD investigators, particularly with respect to the neurobiology of muscular pain, pain in general and neural plasticity, has greatly expanded the understanding of somatic dysfunction[46]. Today's classic discussions on the occurrence and persistence of a given somatic dysfunction concentrate on three different, but potentially overlapping, pathophysiological mechanisms :

(1) Aberrations in neural mechanisms controlling muscles, joints and the autonomic nervous system;
(2) Derangement in circulation and extracellular fluid distribution, including the function of the lymphatic system;
(3) Connective tissue abnormalities.

Current research, using more sophisticated instruments, continues to explore these and other basic neurological considerations. Each model contributes to the understanding of the role of somatic dysfunction in various clinical conditions and the proposed mechanisms by which treatment might benefit each. The section below concentrates only on the neurological aspects and implications of the proposed models and their effect on tissue physiology and function.

### Neurologic relationship to tissue texture abnormalities

The physiological production and maintenance of pain and somatic dysfunction involve

**Table 2** Physiological classification of acute and chronic somatic dysfunction. (From reference 2, page 25)

| *Acute* | *Chronic* |
|---|---|
| *History* | |
| Recent, often an injury | long-standing |
| *Pain* | |
| Acute, severe, cutting, sharp | dull, achy; paresthesias (crawling, itching, burning, gnawing) |
| *Vascular* | |
| Vessels injured, release of endogenous peptides (chemical vasodilatation, inflammation) | vessels constricted because of increased sympathetic tone |
| *Skin* | |
| Warm, moist, red, inflamed (via vascular and chemical changes) | cool, pale (via chronic sympathetic vascular tone increase) |
| *Sympathetics* | |
| Systemically increased sympathetic activity contributes some local vasoconstriction (but local effect overpowered by bradykinins, resulting in overall local vasodilatation due to chemical effect) | has vasoconstriction due to hypersympathetic tone; regional sympathetic hyperactivity; systemic sympathetic tone may be reduced towards normal |
| *Musculature* | |
| Local increase in muscle tone, muscle contraction, hypertonicity and reactivity, increased tone of the muscle spindle | decreased muscle tone; flaccid, mushy; limited range of motion because of contracture |
| *Mobility* | |
| Range often normal; quality is sluggish | limited range, with normal quality in the motion that remains |
| *Tissues* | |
| Boggy edema, acute congestion, fluids from vessels and from chemical reactions in tissues | chronic congestion; doughy, stringy, fibrotic, ropy, thickened; increased resistance; contracted; contractures |
| *Adnexa* | |
| Moist skin; no trophic changes | pimples, scaly, dry, folliculitis, pigmentation (trophic changes) |
| *Visceral* | |
| Minimal somatovisceral effects | somatovisceral effects are common |

both peripheral and central mechanisms. For example, nociception results in local (peripheral) vasodilatation and tissue edema; over time, the central nocifensive and nociautonomic reflexes result in peripheral vasoconstriction, tissue ischemia, altered sweat gland activity and other predictable tissue responses. Thus, local palpatory findings, known as 'tissue texture abnormalities' (TTAs), will depend upon the physiological summation of peripheral and central influences.

Physical, objective findings are palpable and may result from either local or reflex phenomena. The pattern of TTAs present is used clinically to classify somatic dysfunction as acute or chronic (Table 2).

Acute changes arise from a combination of biochemical and neurological responses from irritated or dysfunctional local tissue conditions. The major neurological response to acute somatic dysfunction tends to be an afferent barrage of nociception that appears to feed segmentally related areas in the spinal cord. Use of OMT to modify local somatic dysfunction is often desired in conditions such as low back pain or headache to reduce the amount of nociception and therefore reduce the central perception of pain. Correction of other somatic dysfunctions in these conditions may be initiated locally or in other distant areas to encourage removal of the biochemical irritants.

The neurological models used in research protocols to simulate acute somatic dysfunction focus on a nociceptive element and/or local injury associated with the onset of somatic dysfunction. Typically, coexisting sympathetic autonomic responses (such as vasoconstriction) are overwhelmed by acute stage biochemical mediators (kinins, substance P, prostaglandins, histamine, etc.) resulting in vasodilatation and local edematous swelling, coincident with magnification of pain and muscle irritability. Assigning the designator 'acute' to a somatic dysfunction is based less on the chronology and more on the physiological and palpatory parameters that are measured; this is that period where the biochemical changes out-weigh the autonomic nervous system (ANS) impact, even though both are present.

Acute palpatory TTA findings include: heightened red reflex phenomenon to finger-induced skin friction, palpatory 'bogginess' of the subcutaneous tissues, coexisting increased cutaneous temperature (as measured by palpation or even thermography) and increased sweat gland activity, as well as hyperreactive contraction of local muscles to a given palpatory stimulus (Table 2).

Chronic TTAs develop and progress as the impact of prolonged hyper-sympathicotonia and decreased neural trophism affects peripheral tissues including skin, sweat glands, muscles and capillaries. No longer overwhelmed by acute biochemical changes, early chronic TTAs are considered to be the result of hypersympathetic tone peripherally. Early in the chronic TTA process, the first manifestations are a more rapid blanching of the red reflex response and the presence of palpably cool, sweaty skin secondary to increased sweat gland activity and capillary vasoconstriction[22].

The initial increased skin drag phenomenon as fingers are lightly drawn over the skin's surface from tissues with increased cutaneous humidity will often decrease over time. In the late chronic stage, the palpable skin drag will have gradually diminished and be perceived to be less than normal. Late chronic TTAs are considered trophic changes indicative of sweat gland atrophy concomitant with the development of dry, scaly skin. Low-grade contracture of tissues may also result in loss of trophic substances carried

through neurological and circulatory dysfunction. The residual rapid blanching of the red reflex test coupled with palpably cooler skin suggests continued hypersympathicotonia.

Reflex sympathetic change, prolonged reduction of circulatory homeostasis and reduction of axoplasmic flow may have a significant negative impact on structures and physiological mechanisms far beyond those creating these palpable, more superficial TTAs in segmentally related paraspinal tissues. If this is the case, then finding TTA takes on considerably more clinical relevance, indicating palpable physical clues to underlying problems and reduced health levels. This will be discussed later in this chapter.

The finding of paraspinal somatic dysfunction in which TTA predominates has long been considered by the osteopathic profession to represent a diagnostic branch point. Is the finding primary or secondary? If it is secondary to a viscerosomatic reflex, was the reflex initiated by visceral dysfunction or by visceral pathology? The enormous evidence base that links disorders in all organ systems to predictable, segmentally related sites of somatic dysfunction is incontrovertible[30]. More studies are needed, however, to establish the value in treating both ends of a viscerosomatic or a somatovisceral reflex.

Another clinically correlated finding is a specific form of TTA known as a Chapman reflex[48]. Mapped (Figure 1) as a series of diagnostic points on the anterior surface of the body, the Chapman system was originally derived empirically. More recently it has been the subject of research scrutiny. Each point is

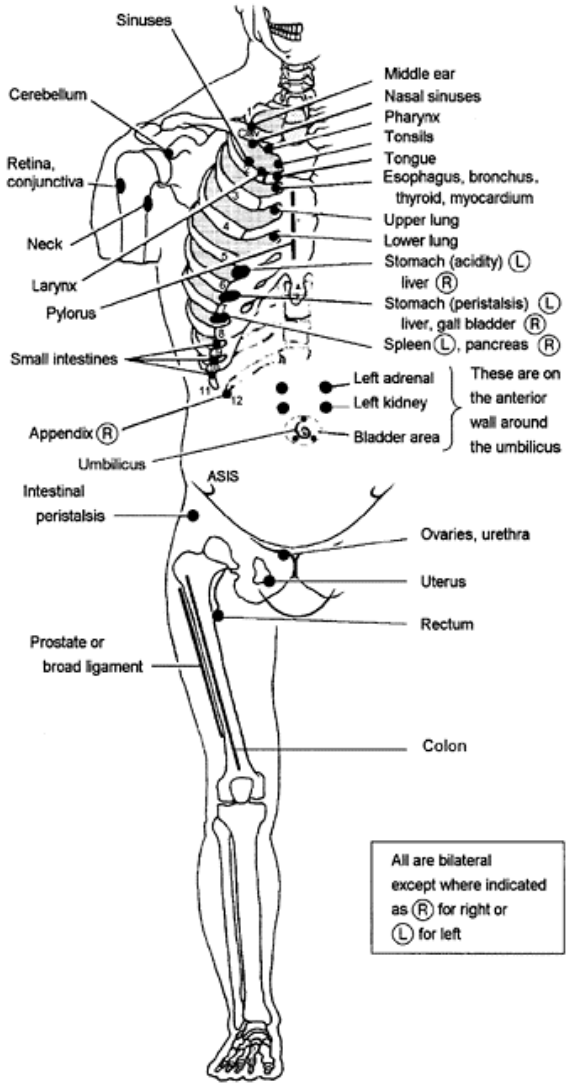


**Figure 1** Anterior Chapman's point chart indicating empirical locations of somatic dysfunction (tissue texture changes) interpreted to reflect a viscerosomatic reflex from the organ indicated. Reproduced with permission from reference 90

2–3 mm in size, locally very tender to moderate palpation and (for those studied to date) seem to average 80% sensitivity and 80% specificity to dysfunction in the visceral structure with which each is linked[49,50]. A Chapman reflex is properly viewed as an additional neuromusculoskeletal clue that is to be interpreted in conjunction with the patient's

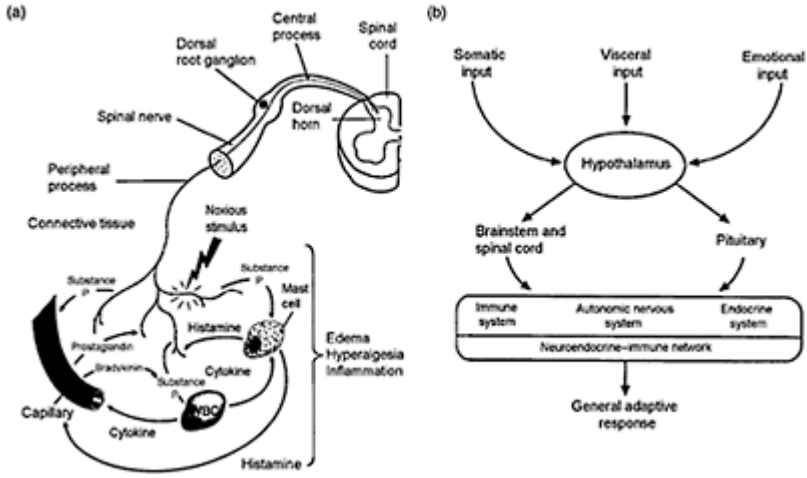


**Figure 2** Models of somatic dysfunction. (a) Interactions between primary afferent fibers and immune system. Noxious stimulus initiates secretion of neuropeptides such as substance P from primary afferent fiber. Result is feed-forward cascade of inflammatory events producing edema and hyperalgesia. (b) Response of neuroendocrine-immune network to signals emanating from somatic, visceral, or emotional dysfunction. Reproduced with permission from reference 142

history and other physical findings. In this context of differential diagnosis, a TTA that is designated 'a Chapman point' is a secondary somatic finding resulting from a primary visceral dysfunction. As such, additional secondary somatic dysfunction would be expected in the segmentally related tissues in other reflexly linked sites, including the paraspinal tissues.

## Neurological models of somatic dysfunction

As might be expected when new information is integrated, existing postulated neurological models for somatic dysfunction evolve. Even long-standing, useful models such as the 'pain-spasm-pain cycle' model are not likely to survive in their simplest of forms, as the complexities of various interactions between central and peripheral nervous systems become better understood[46]. That said, the classic models (Figure 2) that perhaps best lend themselves to understanding the osteopathic approach to treating somatic dysfunction with OMT are:

(1) The facilitated segment and other nociceptive spinal cord reflexly mediated models[22,51,52];
(2) Gravitational strain pathophysiology and other postural muscle imbalance models[53,54];
(3) Allostatic and biopsychosocial models[31,55].

Most probably none of these models functions in isolation. Nonetheless, each is useful in making clinically relevant predictions related to somatic dysfunction.

As previously mentioned, spinal reflex behavior research laid the groundwork for a comprehensive neural model that addresses the cause and substance of many somatic dysfunctions. *Nociceptive models* of somatic dysfunction propose that associated findings, such as tenderness, asymmetry, restriction of mobility, and autonomic, visceral and immunological changes affecting other tissues are produced by pain-related sensory neurons and their reflexes[52]. Sensitization of spinal neurons is a characteristic neurological finding consistent with this model. Spontaneous neural activity appears that is not normally present. Subsequent elevated resting states (decreased thresholds) result in these neurons responding to stimuli that would normally have been subthreshold. It also results in recruitment of so-called silent (non-pain) nociceptors that, under normal circumstances, would be non-responsive to maximal noxious stimuli[30]. In these models, 'wind-up' (especially at the spinal level) is accompanied by recruitment of additional receptive fields, resulting in stimulus-evoked release of neuropeptides. Disturbed sympathetic responses are also measurable[56–58].

In the *facilitated segment model*, self-sustaining abnormal reflexes are postulated to be responsible for the occurrence and persistence of spinal somatic dysfunction. These reflexes begin as afferent neural discharges, initiated by stimulation of proprioceptors or nociceptive receptors in viscera or the somatic tissues that have become dysfunctional or irritated. Constant afferent bombardment of their related spinal cord segments results in facilitation of these spinal cord segments. 'Cross-talk' between visceral and somatic cell bodies in those facilitated cord segments results in increased and inappropriate efferent sympathetic impulses to the tissues innervated by those segments, either somatic or visceral. The facilitated spinal cord segments are then further potentiated by a secondary increase in afferent discharges from the tissues that had received the initial sympathetic bombardment from the facilitated spinal cord segments[27].

An initial trauma does not have to be perceived as pain to launch a vicious reflex cycle. In fact, it has been demonstrated that, once established, spinal facilitation survives transection of the spinal cord[59]. When present, the perception of pain may be caused by factors associated with the increased sympathetic discharge or by the cross-talk that occurs at sites of nerve deformation between the sympathetic postganglionic axons and neighboring unmyelinated sensory fibers. In essence, the facilitated spinal segment model

considers that clinically relevant disturbances, including somatic dysfunction, are caused by aberrations of local and regional feedback mechanisms and appear to be triggered by patterns of sensory signals that have become 'garbled or noisy' because of long-term and/or inappropriate increase of afferent input to the spinal cord from injured, strained, or otherwise impaired tissues (somatic or visceral).

The palpable characteristics of somatic dysfunction and the potential for predictable neurophysiological disruptions in segmentally related somatic and visceral structures were codified by Korr in his series of articles on the 'Spinal Cord as Organizer of Disease Processes'[25–27,60]. He stated that the facilitated spinal segment acts as a 'neurological lens' to focus physiological change from various stresses (physical and emotional) upon segmentally related tissues. The facilitated segment model helps to explain the formation of somatovisceral, somatosomatic and viscerosomatic reflexes. It also makes a rational case for the value of reducing somatic dysfunction (as well as other sensitizing causes) by using OMT as an adjunctive or primary treatment modality in the management of patients with evidence of interaction between somatic and visceral dysfunction.

Czech neurologists Lewit and Janda also make a strong case for identifying and treating somatic dysfunction from the perspective of an *integrated neurological function* perspective (see citations in reference 47). They argue that somatic dysfunction is most frequently the cause of faulty movement patterns potentiated by muscle imbalance and postural-gravitational strain[47]. The body's immediate response is to compensate for, or adapt to, the newly established baseline changes. This further stretches the body's plasticity to a limit beyond which the reaction becomes conscious, especially when it is associated with pain. Simons and colleagues echo a significant part of this model as they approach the diagnosis and treat-ment of myofascial pain and dysfunction[51]. According to these authors, postural imbalance is the most common perpetuator of myofascial dysfunction and pain.

In the muscle imbalance models, a major point is made in recognizing that different muscles have differing fiber responses to prolonged stress. Stressing postural muscles (those typically crossing two or more joints and having a higher percentage of dark, slow twitch fibers) results in a hypertonic response, whereas phasic muscles (those typically acting as antagonists to postural muscles and made up of predominantly fast twitch fibers) will react by becoming pseudoparetic. Such imbalance leads to reflex perpetuation of the muscle dysfunction and alters normal firing patterns of muscle groups used to accomplish coordinated movements. The order of these altered firing patterns can themselves be diagnostic of different underlying dysfunctions[61].

In the *gravitational strain and postural imbalance model*, underlying postural-biomechanical causes must be specifically addressed[53,54]. Furthermore, neurological implications of postural-phasic and agonist-antagonist patterns help guide recommended treatment approaches to the associated myofascial somatic dysfunction[62,63].

(1) First use manual techniques to release overactive or tight muscles to restore their normal length. Muscle energy OMT (post-isometric relaxation) and inactivation of myofascial trigger points are highly recommended[64]; counterstrain OMT and a variety of soft tissue OMT procedures are also advocated[51].
(2) Strengthen muscles that remain weak through directed, individually prescribed exercise protocols. (It has been noted that release of the tight muscles often restores

strength and normal function to reflexly inhibited pseudoparetic muscles, even without further treatment.)

(3) Establish optimal motor patterns through retraining and education.

In somatic dysfunction, even though the initiating event may have been traumatic, it appears that nociceptive stimuli from local tissues play a major role in initiating the spinal cord-level reflexes that, in turn, alter muscle length, tone and balance. Other somatic reflexes then play a role in maintaining and organizing these aberrant reflexes. Finally, because of cross-talk by the spinal cord-level segmental circuitry controlling autonomic and visceral functions, the local somatic findings of altered muscle length, tone and balance are frequently accompanied by segmentally related autonomic and visceral aberrations, completing the symptom complex of somatic dysfunction.

In this manner, the central nervous system (CNS) functions both as an 'integrator' that senses and analyzes the environment, generating command signals along the motor pathways to muscles and other effectors[65], and as an 'organizer' useful in interpreting segmentally related patterns of pain and dysfunction[26,66] (Figure 3). The CNS interprets and assigns differing priorities to afferent nociceptive stimuli[67] with subsequent automatic nocireflexive changes and adaptations largely occurring without conscious awareness. Because not all signals from the peripheral nociceptors reach the level of conscious pain perception, there is wide variability in the pain threshold and perceived pain intensity, even with the same stimulus in the same person[68]. Nonetheless, the barrage of nociceptive stimuli has significant physiological (nociflexive and nociautonomic) ramifications that are capable of manifesting as centrally organized peripheral tissue texture abnormalities. At the spinal cord level, these segmental and suprasegmental circuits maintain muscle length and tone and guide reflexes. Ultimately, short-term and chronic alterations in sensory input to the CNS can result in enduring changes in central processing[69] and recurrent somatic dysfunction[54].

The physiological impact of somatic dysfunction is not limited to pain and peripheral palpatory changes. In addition to initiating protective reflexes and providing the CNS with

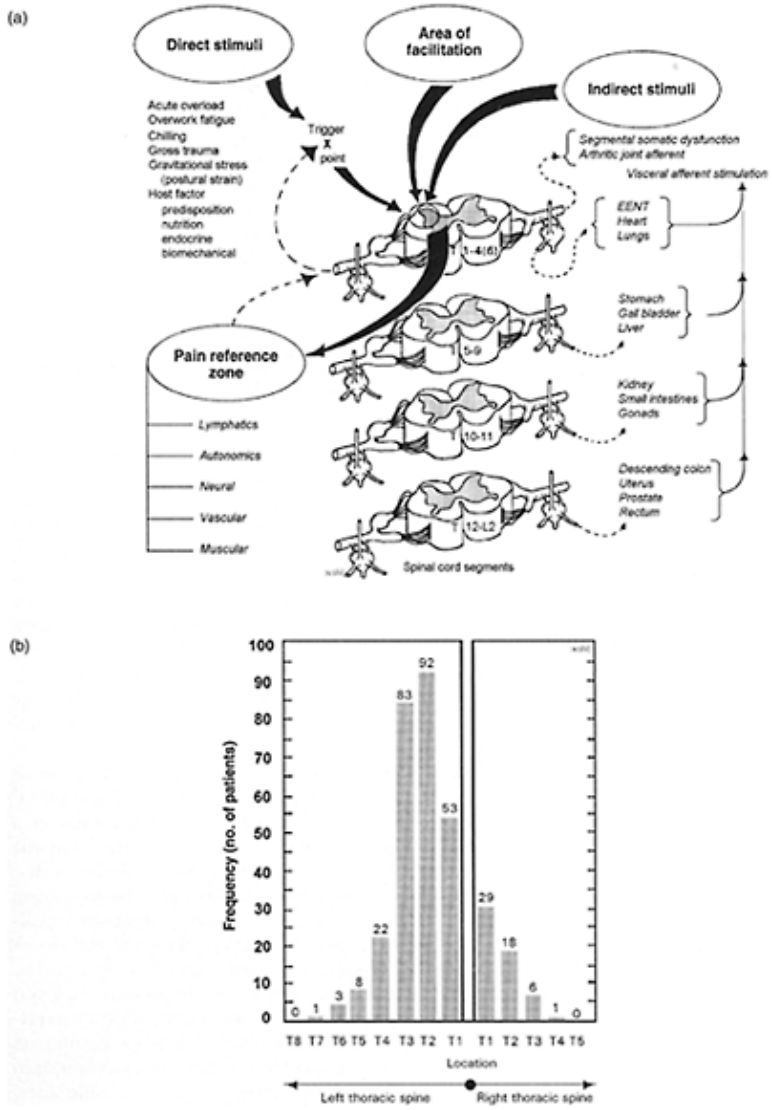


**Figure 3** The spinal cord as organizer of disease processes. (a) General layout; (b) frequency of patients experiencing difficulties from the left and right thoracic spine in 97 subjects with cardiac diagnoses. Reproduced with permission from references 45 and 90

warning signs, noxious somatic stimuli influence the release of extracellular messengers from the endocrine-immune axis[70]. Both circulating humoral factors and the enhanced neural activity summate to initiate general arousal and associated protective endocrine and neural reflexes. This summation occurs primarily at the brainstem level.

In the *allostatic model,* somatic dysfunction, acting through the nervous system, relays an excitatory drive on the locus ceruleus-norepinephrine (LC-NE) and hypothalamicpituitary—adrenal (HPA) axes of the midbrain and hypothalamus[55]. Studies suggest that this same dysfunction also stimulates the HPA axis through release of cytokines and by humeral routes[71]. Subsequent increased activity in the HPA axis results in alteration of levels of adrenal cortical hormones, norepinephrine and other modulators of homeostasis and immune function. Prolonged arousal of these routes, with failure of feedback mechanisms once a threat has passed, leads to an accumulated 'allostatic load'[72] that disturbs normal homeostasis. Increased allostatic load has been correlated with increased cardiovascular disease, complex effects on the immune system and a number of CNS and ANS disturbances. Biopsychosocial/psycho-neuro-immunology models similarly recognize the role of various physical and non-physical stressors in disturbing homeostatic mechanisms, with resultant systemic consequences.

From the perspective of the emphasisis of somatic dysfunction disrupting and modulating homeostasis, the primary therapeutic objective is to restore local tissue function while simultaneously promoting central integration of the resultant afferent stimuli from the region and reducing allostatic load. An osteopathic approach to health promotion includes identifying and reducing sources of chronic exaggerated nociception, introduction of programs to encourage optimal biomechanical alignment and function for the individual, and strategies to deal with physical and non-physical stressors. Long-term objectives seek to optimize tissue-level health through integrated homeostatic mechanisms.

In summary, somatic dysfunction can be a self-limited local phenomenon or it can be related to a variety of perpetuating factors, some neurologically mediated. It is considered both a disruptor of homeostasis as well as an indicator of an underlying neuromusculoskeletal disturbance. Its role in differential diagnosis ranges from a primary disorder to a secondary phenomenon. In addition, from a neurological perspective, it can have a significant influence on the physician's interpretation of historical data and physical findings.

## Somatic dysfunction: effect on neurologic testing outcomes

A wide range of neurological and neuromuscular functions are accurately assessed using standard neurological tests. The pattern of positive and negative findings, coupled with a precise patient history, is critical for identifying the suspected area of pathology. False-positive and -negative tests can confound accurate diagnosis, and somatic dysfunction is capable of producing these as well as other misleading subjective and objective findings. Lessening the impact of somatic dysfunction may significantly enhance the accuracy and diagnostic interpretation of several neurological examinations.

The presence of somatic dysfunction is capable of modifying the result and interpretation of standard neurological findings in a number of ways. For example, certain somatic dysfunctions create pain and dysesthesia that may be misinterpreted as

radicular in nature; others may establish patterns of muscle imbalance in which certain muscles test weak (pseudoparesis). Muscle hypertonicity and/or guarding may reduce the amplitude of a given deep tendon reflex. Immediately after correcting somatic dysfunction, change in certain tests of neuromuscular function is commonplace and therefore warrants serious consideration by those performing the neurological examination.

Muscle somatic dysfunction, especially with a concomitant myofascial trigger point, is often

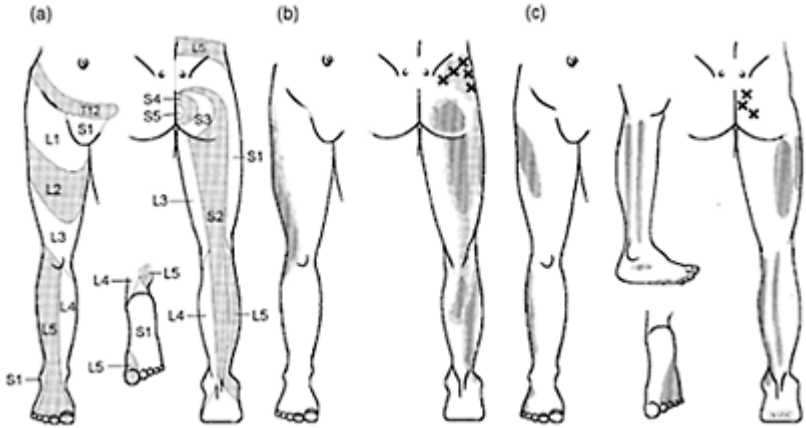


**Figure 4** Differential diagnosis of neuromusculoskeletal causes of lower-extremity referral pain. Examples of (a) dermatomal pattern; (b) gluteal myotomal pattern; (c) posterior sacroiliac ligament sclerotomal

responsible for false-positive interpretations of certain neurological signs and symptoms. Furthermore, certain common patterns of somatic dysfunction mimic the symptoms of common neurological disorders and create altered neurological findings that are misconstrued as supporting the neurological diagnosis. An understanding of somatic dysfunction expands the differential diagnosis required before making the diagnosis of the neurological disorder and expands the therapeutic armamentarium in treating patients complaining of certain symptom complexes.

### *Lumbosacral radiculopathy and sciatica*

Lumbosacral radiculopathy and sciatica are often overdiagnosed or misdiagnosed. In part, this is because several regional somatic structures are capable of mimicking classic pain referral patterns and altering the interpretation of the neuromuscular tests commonly used in the diagnosis of these two entities. Therefore, in the absence of ‘red flags’ and before

ordering expensive imaging tests or making a pathological diagnosis, osteopathic physicians palpate these somatic structures for dysfunction or signs of biomechanical stress.

Figure 4 illustrates the assessment of each of the possible somatic structures involved in the differential diagnosis of this region. Note the similarity in the distribution of an S1 radiculopathy due to a herniated disc, a gluteus minimus myofascial trigger point due to hip dysfunction and posterior sacroiliac ligament strain due to sacroiliac shear somatic dysfunction[54]. Pain patterns are useful in diagnosis but can be deceiving.

Classic neurological tests can also be misleading. Because they are 'phasic' muscles, biomechanically stressed gluteus medius and minimus muscles demonstrate reduced strength when tested. This weakness will often result in a Trendelenburg test that is misinterpreted as a sign of denervation rather than dysfunction[73]. Coupled with the low back pain that usually is seen with dysfunction in this region, patients with a gluteus minimus myofascial trigger point will report a distinctive pain pattern that resembles sciatic or discogenic radiation. It is no coincidence that Travell and Simons refer to myofascial trigger point dysfunction in this muscle group as 'pseudo-sciatica' and its misdiagnosis as a significant cause of 'failed laminectomy syndrome'[74]. Any dysfunction in these muscles

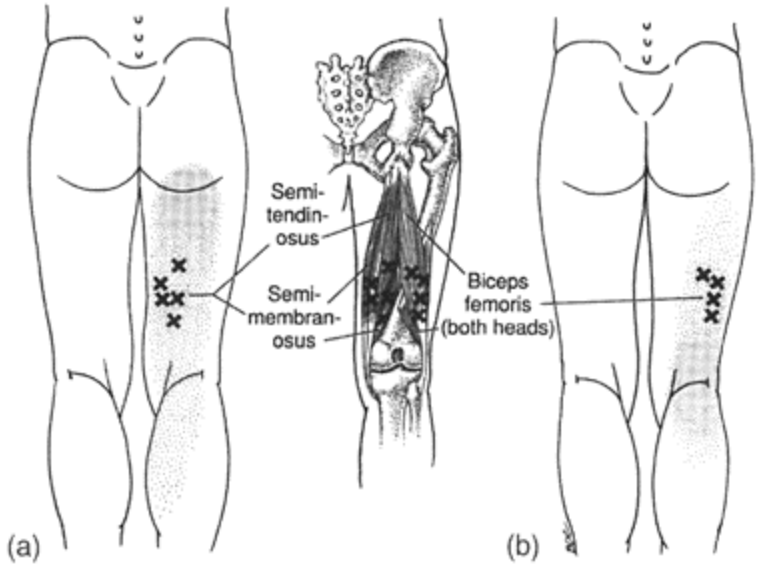


**Figure 5** Hamstring trigger point pain pattern and false-positive neurological testing. (a) Composite semitendinosus and semimembranosus muscles; (b) composite long and short heads of the biceps femoris muscle. Reproduced with permission from reference 75

should be identified and treated, with rechecking of Trendelenburg and/or muscle strength afterwards. After the dysfunction is removed, the patient should be re-questioned to determine whether the pain pattern has resolved.

The commonly employed straight leg-raising test is also fraught with confounders, ranging from sacroiliac joint and hip pain (from dysfunction or pathology) to myofascial trigger points in the hamstrings. Each of these is capable of restricting the total range of motion during the test and creating local and referred pain[75]. Furthermore, false-positive 'verification' is possible using the dorsiflexion of the foot maneuver designed to stretch the sciatic nerve in as much as this motion simultaneously activates myofascial trigger points in the hamstrings (Figure 5). Correction of underlying somatic dysfunction in the sacroiliac joint, hip and hamstrings will provide a more accurate straight leg-raising test.

Sacroiliac joint dysfunction is also capable of placing biomechanical stress on the posterior sacroiliac ligament[76]. This ligament has been shown to create a pain pattern similar to that of the gluteus minimus. Significant stress on this ligament, and the piriformis muscle as well, is seen after certain traumatically induced shearing forces into the sacroiliac joint, creating non-physiological somatic dysfunction (dysfunction that is not a normal part of the motions of this joint while walking, breathing and bending). Often resolution of low back pain with radiation down the leg is delayed until the sacral or innominate shearing dysfunction is corrected. Such somatic dysfunction has been documented by Greenman to be two of the top six diagnoses responsible for recurrent low back pain otherwise unresponsive to conservative care[77].

Piriformis muscle dysfunction is another diagnosis that should be ruled out in patients with a sciatic pain distribution. Travell and Simons document entrapment of the sciatic nerve (or more commonly the peroneal fibers within) with myofascial trigger points in this muscle and the osteopathic literature discusses the piriformis syndrome as having the potential to maintain irritability of the underlying sciatic nerve[78]. In the case of true entrapment, there may be some weakness in testing muscles innervated by the peroneal nerve and the

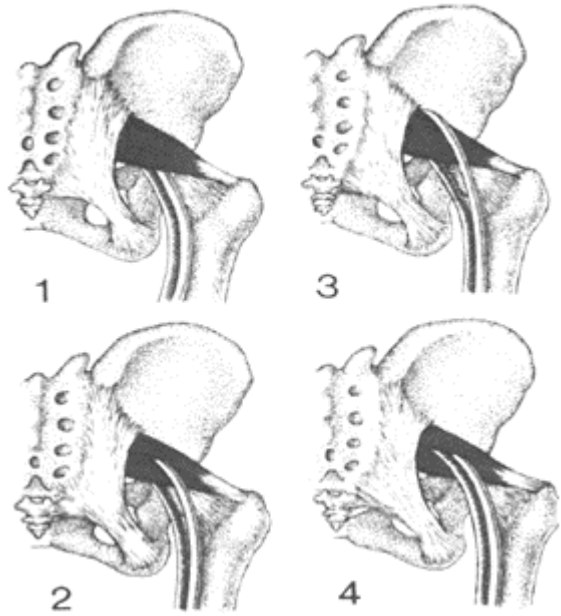


**Figure 6** Anatomic variations of relationship between the sciatic nerve and the piriformis muscle: neurologic implications of piriformis somatic dysfunction vary with structure as does treatment with injection therapy. (1) Typical relationship in 85% of population; (2) fibular (peroneal) portion of sciatic nerve passes through muscle in 10% of Caucasian population or 30% of population of Asian descent; (3) variation with fibular portion above and then posterior to the piriformis is seen in 2–3% of population; (4)variation <1%. Reproduced with permission from reference 78

patient may notice a slight foot drop when tired. Other critical diagnostic findings include ipsilateral external hip rotation and palpable hypertonicity generally with the potential for local myofascial trigger points (Figure 6). Tenderness over the sciatic nerve without these

palpable changes in the piriformis muscle or its function would rule out piriformis dysfunction as the cause of the symptoms[2].

A final caveat in this discussion is offered based upon the multiple models applied to diagnosis and treatment in this region; co-existing and overlapping diagnoses are quite common here. True radiculopathy predisposes to secondary myofascial trigger points in the muscles that derive their innervation (and neurotrophism) from the involved root; sacroiliac shearing dysfunctions create significant muscle imbalance and distort origin-insertion relationships that can lead to secondary or recurrent piriformis dysfunction[79]; and weakness in the glutei reduces 'force closure' of the sacroiliac joint leading to instability and posterior sacroiliac strain[80].

A variety of effective OMT techniques can be applied to correct sacroiliac, gluteus and piriformis dysfunction[81]. Because of the potential for co-existing pathology, dysfunction in the presence of preliminarily positive neurological testing is most commonly treated with counterstrain, indirect myofascial release, or muscle energy techniques. For pelvic shearing somatic dysfunction, a gentle springing or, occasionally, a direct reversal of the traumatic shearing forces will provide dramatic relief. Care in positioning to avoid aggravation of any existing dysesthesia or pain is the rule. A more complete description of an osteopathic approach to lower motor neuron disorders will appear at the end of this chapter.

### *Other common neurological tests and syndromes with somatic differentials*

As noted above, an important component of the osteopathic approach to patients presenting with signs and symptoms of what might be a neurological disorder involves ruling out and/or treating certain somatic dysfunctions considered to be important in the differential diagnosis or that might confound the neurological tests used. In definitive neurological disorders, the co-existence of somatic dysfunctions that produce similar symptoms makes the diagnosis and treatment of somatic dysfunction in these patients an important component to be considered.

The constraints on the length of this chapter do not allow the use of the same level of detail as used in the previous section concerning radiculopathy and sciatica. Table 3, however, provides a partial list of entrapment neuropathies, neurological tests that might be altered by certain somatic dysfunctions, and pain and dysfunction patterns that are similar to neurological disorders[4,40,51,82,83]. While

**Table 3** Examples affecting differential diagnosis

| *Condition* | *Somatic dysfunction (SD) with similar presentation. Should be ruled out or, if present, treated first* |
|---|---|
| *Examples of upper extremity entrapment neuropathies* | |
| Median nerve | carpal tunnel, pronator teres muscle, anterior interosseous membrane |
| Ulnar nerve | ulnar general: cubital tunnel, canal of Guyon, thoracic outlet, first rib, flexor digitorum muscle, flexor carpi ulnaris muscle ulnar deep motor branch: opponens digiti minimi muscle |

| | |
|---|---|
| Radial nerve | radial general: triceps brachii muscle<br>radial sensory: brachialis muscle<br>radial superficial sensory: supinator muscle<br>radial deep: middle scalene muscle |
| Musculocutaneous nerve | coracobrachialis muscle |
| Brachial plexus | anterior and middle scalene muscles lower trunk: thoracic outlet, first rib, scalene trigger points, pectoralis minor muscle |
| *Examples of lower extremity entrapment neuropathies* | |
| Sciatic nerve (sciatica) | piriformis syndrome or trigger point |
| Common peroneal (fibular) nerve | fibular head posterior SD |
| Posterior tibial nerve | tarsal tunnel |
| *Examples of nerve entrapment neuropathies (cranial* | |
| Greater occipital nerve | semispinalis capitis muscle |
| Cranial nerve VI (medial strabismus) | petrosphenoidal ligament secondary to temporal SD |
| *Examples of altered neurological sign/test* | |
| Muscle strength tests | myofascial trigger point or prolonged strain in that phasic muscle |
| Straight leg raising | myofascial trigger point hamstrings |
| Extraocular muscle testing | petrosphenoidal ligament secondary to temporal SD |
| Balance tests | sternocleidomastoid myofascial trigger point temporal bone SD |
| Sciatic posturing | psoas syndrome |
| *Examples of similar pain or dysesthesia patterns* | |
| L5, S1 radiculopathy | gluteus minimus myofascial trigger point posterior sacroiliac ligament strain |
| Migraine cephalgia | trapezius myofascial trigger point sphenosquamosal pivot SD |
| Carpal tunnel syndrome | forearm myofascial trigger points |
| Brachial plexopathy | scalene trigger points, first rib SD |
| Sciatica | piriformis syndrome |

varying degrees of documentation exist for items listed, the couplings are clinically useful in teaching osteopathic students to broaden their differential diagnosis and it takes only a few extra minutes to evaluate and treat as needed to obtain a more accurate diagnosis. The potential for recurrence of the somatic dysfunction and/or the neurological findings are dependent upon whether the clinician discovers and treats both the primary cause and any perpetuating factors. At the end of this chapter an osteopathic approach to

a few of the above disorders will demonstrate that OMT is sometimes a primary treatment and often an adjunctive treatment.

## TREATING SOMATIC DYSFUNCTION

In the USA, a physician capable of fully assessing risk/benefit ratios and cost-effectiveness of all potential treatment modalities directs the OMT prescription, if indicated, and its implementation. A complete manual medicine education is also extremely important for assessing its place in the total management of the patient and selecting the type of manual method, activating force, frequency and duration of this form of treatment. Individual characteristics of the somatic dysfunction, the biopsychosocial aspects of the patient-as-a-whole, any other underlying pathophysiological processes and the skills of the treating physician dictate many of these choices.

Physicians incorporating an osteopathic approach to OMT specifically ponder the following:

(1) *Goal:* What area or physiological process would benefit from OMT? Is there an acceptable risk/benefit ratio to consider such an approach?
(2) *Method:* What methods or techniques of OMT are indicated and contraindicated (direct, indirect, or combined)?
(3) *Activating force:* Which would be the most appropriate (muscle energy, inherent force, patient co-operation, high velocity-low amplitude thrust)?
(4) *Dose:* What are the underlying homeostatic reserves of the patient and what duration of treatment administration would provide maximum benefit?
(5) *Frequency:* How frequently should the manipulation be repeated within the parameters of patient response and costefficacy?

The OMT prescription[40] takes form after appropriate evaluation and establishment of a working diagnosis by a knowledgeable and skilled physician who then seeks to accomplish a definable therapeutic goal. As with most prescriptive care, in subsequent visits the patient is re-assessed for symptomatic and physiological change including a re-examination for somatic dysfunction prior to the decision being made to re-initiate or not initiate the next manipulative treatment. Clinical outcomes, patient response to the previous treatment and visitspecific findings of somatic dysfunction influence the goals and help the physician make decisions about manipulative frequency, methods and dose used in follow-up visits.

Limiting factors[2,84] considered in the formulation of an OMT prescription and its delivery include:

(1) *Patient-centered factors,* including the knowledge or concern of the patient's ability to respond because of age, sex, size, occupation, present health, dietary or life-activity risk factors, allostatic load (including biopsychosocial stressors), support system, allergies to potential treatment alternatives and response to similar treatments or modalities given in the past.
(2) *Disease-centered factors,* especially those accompanied by osteoporotic, rheumatological, orthopedic, neurological, cardiovascular or oncological change. Even

without specific diagnosis, signs or symptoms of other acute or chronic pathophysiological processes affecting the neuromusculoskeletal or related systems must be considered. These conditions often dictate treatment position, the manual medicine method or activation employed, and treatment duration and frequency.

(3) *Physician-centered factors*[84], including the ability of the physician to accomplish the treatment or to refer the patient appropriately for that form of care. Other factors might include personal stature, training, specialization background, license limitations and ability to maintain advances made in the manual medicine field through continuing medical education.

The International Federation of Manual/ Musculoskeletal Medicine (FIMM) recommends a core training of approximately 300 postgraduate hours for MDs to gain basic proficiency, safety and efficacy. The American Academy of Osteopathy and several colleges (Philadelphia College of Osteopathic Medicine and Michigan State University College of Osteopathic Medicine) have organized ongoing programs for MDs to gain these skills. Osteopathic pre-doctoral education provides similar expertise under the supervision of OMM specialists. In the osteopathic profession, further residency training in neuromusculoskeletal medicine can lead to certification as a specialist in this field. Specialists with outstanding skills in OMT are typically designated with C-SPOMM, C-OMM, or CNMS (all equivalent) or by the designation FAAO (fellow in the American Academy of Osteopathy) that requires the certification designation first and then requires additional credentialing in the field.

Once it is decided that the modality itself should be used for the benefit of the patient, OMT is carefully selected based upon a variety of host factors that determine the risk/benefit ratio of differing forms of technique (Table 4). In general, manipulative treatment is among the safest treatments that a physician can administer (serious adverse response report 1:400000 to 1:1000000)[85].

An osteopathic approach that integrates palpatory diagnosis and considers a role for OMT adds a different perspective to the management. The remaining section of this chapter focuses on an osteopathic approach to some common examples of neurologically related clinical conditions in which: *somatic dysfunction* plays a major role in either etiology or differential diagnosis; and OMT *techniques* are frequently useful in removing somatic dysfunction to improve clinical outcomes or patient satisfaction.

## Lower motor neuron disorders

This includes peripheral and cranial nerve entrapment neuropathies as well as both cervical and lumbar radiculopathies.

Somatic dysfunction is a prominent finding in those patients referred for electromyography (EMG) who are suspected of having lower motor neurological problems. Although studies have not been performed to determine whether such somatic dysfunction was a predisposing, causative, or simply a secondary finding, it is present and thereby warrants consideration in the differential diagnosis of symptoms and potential treatment. It has been postulated that articular and myofascial somatic dysfunction may occur with biomechanical strain or with overuse[46]. Both conditions have been shown to arise through altered joint and muscle activity within the myotatic unit as the patient substitutes or compensates to accomplish functional tasks or to avoid pain.

In this section, carpal tunnel syndrome and sciatica secondary to piriformis syndrome will serve as examples of osteopathic approaches to the treatment of patients with lower motor neuron conditions in which OMT is incorporated. Cervical and lumbar radiculopathies will also be discussed where, in many situations, the role of OMT becomes an adjunctive conservative treatment. OMT to the region in these patients with certain techniques constitutes a relative contraindication in only a few specific circumstances.

### *Diagnosis and treatment of carpal tunnel syndrome*

Carpal tunnel syndrome is traditionally described as resulting from pressure on the median nerve as it passes with the flexor

**Table 4** Clinical experiences modifying osteopathic manipulative treatment (OMT)

| *Question or option* | *Clinical experience (generalities and guidelines only)* |
|---|---|
| Selection of direct or indirect method? | Direct techniques may be especially helpful in somatic dysfunction with chronic changes such as fibrosis<br>Indirect or direct techniques are of no value to a physician who lacks the skill to use that technique[84]<br>Indirect techniques may be especially helpful in somatic dysfunction manifesting acute, edematous tissue texture changes |
| How much force should be used in an HVLA thrust? | '…enough to affect a physiological response (increased joint mobility, produce a vasomotor flush, produce palpable circulatory changes in periarticular tissues, and/or provide pain relief) but not enough to overwhelm the patient.'[40] |
| Parameters modifying dose or frequency in OMT?[84] | The sicker the patient, the lower the dose<br>Pediatric patients can be treated more frequently<br>Geriatric patients require a longer interval between treatments to respond<br>Acute cases should have a shorter interval between treatments initially |
| General guidelines for treatment order based upon regional affects? | In the chest cage, generally treat somatic dysfunction in this order: thoracic vertebrae, ribs, sternum<br>In the pelvis, generally treat 'non-physiological' somatic dysfunctions (shears) prior to other dysfunctions<br>For very acute somatic dysfunction, it may be necessary to treat secondary or peripheral areas first, to allow access to the acute site<br>In lymphatic goals, open fascial drainage pathways before enhancing the effects of diaphragmatic or augmented lymphatic pumps; local effleurage or other local tissue drainage is best done after other lymphatic techniques designed to achieve tissue drainage |
| What side-effects alert the clinician to modify OMT? | If the patient reports a flare-up of discomfort for more than 24 h, modify the dosage, choice of activating method and/or duration of treatment, as needed<br>In set-up and activating phases, it is best to avoid certain positions that aggravate otherwise intermittent radiculopathic signs (cervical or lumbar spine) in patients with spinal degenerative joint disease (DJD) or herniated nucleus pulposus |

| | |
|---|---|
| | Care must be paramount if high-velocity, low-amplitude thrust OMT (HVLA) is selected in a patient suspected to harbor significant osteoporosis; often forward bending pressures should be avoided as well |
| Guidelines: how long to treat? | Chronic conditions usually require more than one treatment; one rule of thumb suggests that it may take as many treatment sessions as years of dysfunction<br>Caring, compassionate novices often err on the side of overdosage |
| Risk/benefit issues? | An appropriate assessment and diagnostic examination before, during, and after OMT permits accurate risk/benefit decision-making regarding indications, relative contraindications and absolute contraindications<br>Manipulative treatment is among the safest treatments that a physician can administer (serious adverse response report 1:400000 to 1:1 000000)[85] |

tendons of the fingers through the tunnel formed by the carpal bones and the transverse carpal ligament. This can result from a number of different etiological factors and several known pathophysiological mechanisms play a role in precipitating, perpetuating and/or aggravating this condition. An OMM evaluation of the patient with carpal tunnel syndrome is therefore designed to determine all systemic or host factors that might have contributed to the underlying cause of this syndrome and to examine for biomechanical factors that might interfere with homeostatic mechanisms or otherwise perpetuate the condition.

OMM goals for a treatment plan are individually tailored for each patient. For example, the amount of emphasis and any subsequent OMT applied will be very different for those with underlying endocrine problems (such as hypothyroidism) than for those with overuse or some other biomechanical causes.

Likewise, because edema at the wrist is capable of creating or perpetuating the syndrome, OMM evaluation seeks to determine whether tissue congestion exists, whether it is local, regional, or systemic, and whether homeostatic mechanisms for enhancing removal of edematous fluid are capable of providing maximal function if needed. If upper extremity edema is present, an osteopathic approach might choose to center upon accomplishing respiratory-circulatory goals[86] to maximize fluid drainage of the upper extremity.

In examining another possible mechanism, coexisting radiculopathy or proximal neural entrapment neuropathies have been implicated in decreasing axoplasmic flow needed to provide trophic factors required in the periphery. This so-called ‘double-crush’ phenomenon[87] may account, in part, for the 10% of patients with CTS who are found to have a primary cervical radiculopathy[88]. Treatment of coexisting proximal pathology may require integration of pharmacological, physical therapeutic and/or surgical elements. In like manner, however, somatic dysfunction of the cervical region has been postulated[47] to have the capability of contributing to a form of double crush phenomenon that would be amenable to OMT. Such a study is currently inthe planning stages.

Regardless of the underlying cause or proposed mechanisms, the high incidence of somatic dysfunction[89], its role in the differential diagnosis of this condition[51], and its ability to compromise a variety of homeostatic mechanisms[90] constitutes a good reason for including OMT as an adjunct in the treatment of patients with carpal tunnel syndrome.

The findings of somatic dysfunction in patients with carpal tunnel syndrome and the adjunctive role of OMT in treating them are recorded in a number of sources[51,89,91–95]. In one case series of sequential patients presenting for upper-extremity EMG, a second blinded osteopathic physician conducted an osteopathic structural examination. Regardless of the final neurophysiological diagnosis, all subjects had varying combinations of cervical, thoracic, costal and upper extremity joint somatic dysfunctions. However, those with median nerve entrapment neuropathy at the wrist (carpal tunnel syndrome) had a highly significant increased prevalence of myofascial somatic dysfunction in the forearm muscles[89]. The documented pattern of latent and active myofascial trigger points in the anterior forearm included pronator teres as well as the wrist and finger/thumb flexor muscles. Furthermore, better outcomes were seen when OMM protocols were included to expand traditional conservative care consisting of wrist splints, patient education and non-steroidal antiinflammatory drugs (NSAIDs). OMT in these protocols specifically addressed the myofascial trigger points (Figure 7) as well as the articular dysfunction found in the cervical, thoracic, costal and upper extremities. The group of patients who received OMT as part of their management had improved outcomes, including resolution of Phalen's sign, fewer night awakenings, and even a trend toward improvement of palmar (sensory) distal latencies on nerve conduction studies[92].

A number of OMT techniques have been shown generally to be effective modalities in treating myofascial trigger points, a specialized form of somatic dysfunction[96]. The definitive

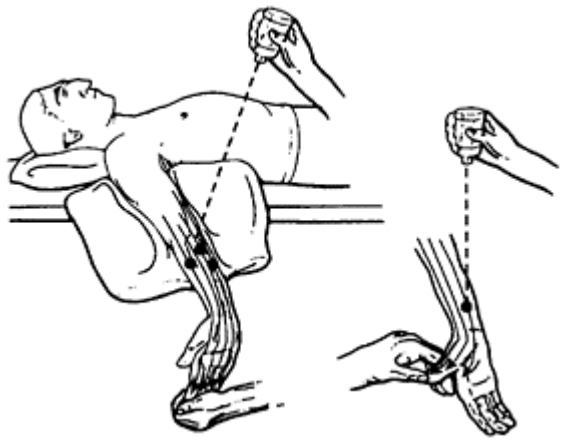

**Figure 7** Removal of forearm myofascial trigger point somatic dysfunction commonly seen in carpal tunnel syndrome

texts on myofascial trigger point treatment specifically note the efficacy of using manual medicine techniques as are applied by many manual professions. These techniques

include direct isometric muscle energy, indirect counterstrain and direct high-velocity-low-amplitude techniques as well as soft tissue techniques such as stretching, kneading and inhibition.

### *Sciatica and piriformis syndrome*

Piriformis dysfunction is not unique with respect to entrapment of neural, vascular, and/or lymphatic structures (Table 3). Examining this entity, however, does provide insights for better understanding of neurological entrapment and the clinical impact of removing underlying somatic dysfunction.

As was stated previously, significant anatomic variability exists with respect to the pathway of nerve fibers within the sciatic nerve and their relationship to the piriformis muscle (Figure 6). Hypertonicity or myofascial trigger points in this muscle are capable of initiating signs and symptoms of entrapment neuropathy. This is especially true for the peroneal fibers, because they are located more superficially within the sciatic nerve or may pass through the belly of the main piriformis muscle mass.

A number of biomechanical and/or somatic dysfunctions can lead to hypertonicity of the piriformis muscle that, in turn, may or may not lead to neural entrapment[2]. Direct irritation from sitting for a prolonged time on a billfold or toilet seat has been documented to initiate this process. Similarly, a sudden stretch of this external hip rotator muscle consistent with a sports injury wherein a cleated shoe may anchor the lower extremity as the athlete turns or is tackled can initiate piriformis dysfunction and sciatica. Piriformis hypertonicity can also result from a number of intrapelvic (sacroiliac joint) somatic dysfunctions, including a sacral shear, or significant hip joint somatic dysfunction.

The efficacy for treatment of the piriformis (and the underlying causation for either its hypertonicity or its trigger point) has been demonstrated in a number of studies. These demonstrated not only alleviation of pain and improvement in neurological function but also improved pelvic floor function and even improvement of certain gastrointestinal and genitourinary functions.

Piriformis hypertonicity responds well to both direct or indirect OMT techniques, and understanding the difference is helpful in understanding how different postulated neurological mechanisms might be used successfully to treat somatic dysfunction with OMT. Counterstrain technique is an indirect method of treatment wherein the muscle harboring a tender point is shortened until deep pressure on the most tender point in the muscle is gone or elicits not more than a maximum of 30% of the original discomfort from a digital provocation. This position is then held for at least 90 s with the finger monitoring the same site but without pressure or other nociceptive input. The relationship between piriformis origin and insertion is then slowly returned to a new and improved resting length without any voluntary assistance on the part of the patient[97]. This technique almost uniformly results in resolution of the tenderness over the muscle belly and return of normal tone to the muscle itself. Conversely, a direct method could be used where the origin and insertion of this muscle is separated (with adduction and internal rotation positioning). In this form of treatment, resolution of the dysfunction is typically accomplished either by employing a series of post-isometric relaxation (muscle energy OMT) maneuvers or by using a vapocoolant spray postulated to distract the CNS while

the physician stretches the muscle further[51]. With precise positioning that is specific and consistent with each technique (even though taken in opposite directions) it is postulated that different neurological mechanisms can be called into play to modulate the central response to peripheral input from different receptors within the somatic tissues. Regardless of the mechanism, the resultant outcome is reduction or resolution of the palpable somatic dysfunction and improvement in the signs and symptoms of any secondary entrapment.

### *Cervical and lumbar radiculopathies*

Radiculopathies are capable of causing recurrent secondary somatic dysfunction as well as myofascial trigger points. More than one postulated mechanism has been advanced for this phenomenon and probably both conditions are simultaneously active. As previously mentioned, radiculopathy may play a significant role through the *double-crush phenomenon.* Here the structural pathophysiological factors at the root level reduce the neural trophic factors available for the peripheral tissues predisposing them to dysfunction and the development of myofascial trigger points. Compared to the muscles in the general population, the incidence of myofascial trigger points is known to be significantly higher in those muscles innervated by the involved root. Likewise, the weakness commonly seen in partially denervated muscles requires biomechanical compensation to accomplish tasks of daily living. This in turn leads to both overuse syndromes in other muscles functioning within the myotatic unit and joint stress due to suboptimal biomechanics in the altered movement patterns.[46]

Somatic dysfunction has been postulated to contribute to the symptomatology of certain radiculopathies. For example, forward-bending somatic dysfunction has a tendency to place increased pressure on the anterior aspects of the vertebral body that would theoretically increase the posterior or posterolateral interdiscal pressure in radiculopathies due to herniated discs. Conversely, backwardbending somatic dysfunction or those dysfunctions with sidebending to the side of a radiculopathy caused by osteoarthritic spurring would theoretically decrease the area of the intervertebral foramen[2]. It is also postulated that somatic dysfunction above and/or below the level of a radiculopathy increases the amount of motion and stress on the remaining segments, including the site of the level of the root pathology[98]. For these reasons, reduction of somatic dysfunction in patients with documented radiculopathy makes sense.

An uncomplicated radiculopathy is not an absolute contraindication to OMT—even at the site of the herniated disk or osteoarthritic spur. For instance, manual traction is often used successfully to reduce radicular symptoms or to assess the reaction of the tissues and patient to other forms of traction. Furthermore, the availability of both direct and indirect OMT techniques permit spinal positioning that can ameliorate the somatic dysfunction without aggravating or irritating the radiculopathy itself.

A well-controlled, randomized series of clinical trials of Swedish patients with low-back pain (with crossover)[99] was conducted between 1992 and 1994. Subjects treated with manual medicine techniques (direct method, lateral recumbent lumbar technique by a physician) in conjunction with other conservative approaches did better than those treated with conservative orthopedic modalities and than those for whom stretching by physical therapists was added. Interestingly, the response to manual treatment was even

more significant in those subjects who had symptoms referred to the lower extremity[99,100], a group often excluded from manual medicine protocols. The best results would appear to be obtained with a combined approach that incorporated the physician-level manipulation and injections, as needed.

It should be emphasized that a number of texts list herniated discs with radiculopathy as an absolute contraindication to 'manipulation'. However, in these texts manipulation is more narrowly defined as the high-velocity-low-amplitude thrust technique. Other manipulative techniques can be and have been successfully used to address mobility in the region of herniated discs.

## Osteopathic considerations in integrated neurological function

As with many clinical topics, it is difficult in an osteopathic approach to separate out a single aspect of diagnosis or treatment from the impact on the rest of the 'body unit' or at least the immediately related ones. Thus, the topic of integrated neurological functions is perhaps appropriate for discussing the clinical application of osteopathic principles, OMT and OMM to health care as delivered by the osteopathic practitioner.

The osteopathic practitioner recognizes that few pathways or homeostatic mechanisms exist in isolation, and therefore striving to optimize integrated functions for the entire patient and recognizing their impact on quality of life issues are central themes in the osteopathic approach[91]. When palpatory diagnosis identifies a given somatic dysfunction, a significant amount of additional diagnosis becomes essential. The integrated nature of somatic dysfunction requires examination of the segmentally related neural, vascular and lymphatic elements. The multifactorial causes of somatic dysfunction suggest the need to examine the visceral system for viscerosomatic causes as well as somatovisceral consequences of the somatic dysfunction. Finally, biomechanically linked elements of the somatic system should be examined for various patterns of somatic dysfunction in arthrodial and myofascial tissues that might indicate that isolated treatment of the somatic dysfunction would be ineffective without treating the larger issue of how the body region or unit is being stressed or overworked.

OMT is only occasionally applied to a single significant somatic dysfunction for its local effect. An osteopathic clinical encounter is rarely complete until, by continued treatment, the patient has reached his or her maximal optimization for that visit, as assessed by local, regional and systemic evaluation. (As an example, after successful treatment of the lumbopelvic region, the patient will often be reevaluated to determine the impact of its removal on functional lower extremity length and posture to determine whether more treatment is required during that encounter.) Patient education and advice concerning follow-up care or specific movements (to be added or avoided) are often added to maintain the effect of the OMT until the changes made in the peripheral input are integrated centrally.

An osteopathic approach that integrates OMM is possible in almost any clinical encounter. However, the final portion of this chapter focuses on a few clinical examples to demonstrate the integrated use of OMT in situations that either affects integrated neurological functions such as reflex phenomena between the soma and the viscera, or impacts on outcomes in conditions commonly seen in a neurologist's practice.

### *Headache*

Headache is a common symptom resulting from many etiologies—ranging from visceral to somatic and from metabolic to idiopathic. Seasoned neuromusculoskeletal clinicians are also attuned to the cervical spine that may play a central rather than a secondary or non-contributory role. The International Headache Society (IHS) includes the cervical spine in its classification schema[101].

According to the IHS, inclusion criteria for the cervical spine features several of the T-A-R-T characteristics used to diagnosis cervical somatic dysfunction:

(1) Local neck or occipital pain projecting to forehead, orbital region, temples, vertex or ears;
(2) Either diminished cervical motion, abnormal cervical contour, texture, tone or response to active and passive stretching and contraction; or abnormal tenderness of neck muscles;
(3) Radiographic evidence of pathology and abnormal posture; or reduced range of motion.

Multiple sources are capable of contributing to the perception of 'headache'. Table 5 denotes some of the common headache causes and the osteopathic consideration associated with each[102].

Recent attempts to document the interrelationship between articular and myofascial components and to link them to relevant historical and physical findings have expanded our understanding of the diagnosis and treatment of the suboccipital region. For example, *Travell and Simons' Myofascial Pain and Dysfunction* points out the common combination of $C_0$, $C_1$, and/or $C_2$ articular somatic dysfunctions found in patients with semispinalis capitis trigger points (myofascial somatic dysfunction)[51]. The combination of articular and myofascial somatic dysfunction is common, as are patterns of somatic dysfunction in functional units.

Other examples link patterns of somatic dysfunction with specific headache presentations. Greenman[77] reported that the majority of patients presenting with cervical spine stiffness and associated hemi-cephalgia running from the occiput to the retro-orbital area were found to have the following palpable structural diagnostic findings:

(1) Left occipitomastoid suture restriction;
(2) $C_0$ (OA) sidebent right, rotated left ($S_RR_L$);
(3) $C_1$ (AA) rotated right;
(4) C2–3 extended, rotated and sidebent left (E RLSL).

Likewise, Kappler reported that a referred retro-orbital pain pattern, consistent with Travell and Simons' upper semispinalis capitis (location 2) trigger point (Figure 8), is often palpated on the anterior portion of a rotated C1 somatic dysfunction[103]. In a population of patients with cervicogenic headaches, 91% of patients had $C_0$ or $C_1$ articular somatic dysfunction and 56% had trigger points in the semispinalis capitis muscle predominantly ipsilateral to the symptomatic side[104].

Palpatory diagnosis for somatic dysfunction is therefore useful in identifying a significant number of the primary musculoskeletal and cervicogenic causes of headache where co-existence of articular and myofascial dysfunction is common. Because soft tissue dysfunction often alters articular motion characteristics in the craniocervical

junction, this author prefers to diagnose and address any soft tissue dysfunction prior to attempting a definitive articular diagnosis through specific segmental examination.

Others find that treatment of articular somatic dysfunction addresses both articular and myofascial components at the same time. Regardless of the varied sequences, treatment of the somatic dysfunction (articular and myofascial) with OMT has been demonstrated positively to affect patient satisfaction[105] and to reduce the level of pain in patients with cephalgia[51].

### *Low back pain*

Patients present to neuromusculoskeletal medicine physicians with low back (lumbopelvic) pain more so than with any other area of the body, with the possible exception of headache. These physicians have moved significantly beyond the historically unifocal preoccupation with discogenic back pain[106]. Farfan, for example, described the cause of low back pain as mechanical with numerous pain generators influenced by biomechanical stress and strain[107]. In the low back, the key pain generators are the somatic dysfunctions of the lumbar zygopophyseal joints[108,109], the muscular elements associated with lumbopelvic function and dysfunction[74] and the sacroiliac joint itself[110,111]. While the latter component is perhaps the most 'controversial'[77], sacroiliac joint dysfunction is acknowledged to play an 'incontrovertible'[112] role in a number of locally painful spinal disorders. Furthermore, Travell

**Table 5** Osteopathic considerations in varying causes of cephalgia

| *Structure involved* | *Stimulation* | *Headache syndrome* | *OPP/OMT approach* |
|---|---|---|---|
| *Extracranial* | | | |
| Scalp and neck muscles | sustained muscle contraction (reflex or psychogenic); local myofascial point (microtrauma/ macrotrauma, reflex or overuse) | muscle contraction headache; myofascial (travel) trigger point headache | decrease stress/tension; relax muscle contraction; eliminate myofascial trigger points as well as Jones' counterstrain points at C1, C2, C4, C5 occipitomastoid, squamosal, infraorbital and nasal; correct cervical and upper thoracic sites somatic arthroidal dysfunction; improve lymphaticovenous drainage of head and neck structures |
| Cranial bones and sutures | impaired or altered craniosacral motion; microtrauma/ macrotrauma | cranial headaches; cephalgia after head trauma | restore mobility between cranial bones; remove somatic dysfunction |
| Cervical vertebral units | impaired or altered cervical motion; microtrauma/ | cervicogenic headaches; spondylogenic | restore mobility and/or stability of cervical vertebral units; remove somatic dysfunction |

| | | | |
|---|---|---|---|
| | macrotrauma | headaches | |
| Mucosa of sinuses | inflammation; pressure change | referred sinus headaches | modify cranial nerve (CN) V nociception; decrease T1 to T4 sympathetic activity; improve lymphatic drainage from head and neck structures; thin sinus secretions (CN VII) |
| Eyes | inflammation; increased intraocular pressure | iritis; glaucoma | **OMT adjunctive;** improve lymphaticovenous drainage; decrease T1 to T4 sympathetic nerves |
| Stomach | reflex referral | gastric headache with or without nausea and vomiting | **OMT adjunctive;** calm (CN X), occipitoatlantal, atlantoaxial, C2 and occipitomastoid somatic dysfunction; OMT to T5 to T9 and celiac ganglion |
| Lung/bronchi | reflex referral | pulmonary headache | **OMT adjunctive;** calm (CN X), occipitoatlantal, atlantoaxial, C2 and occipitomastoid somatic dysfunction; OMT to T2 to T6 |
| Blood vessels | inflammation; dilatation | migraine; cluster headache (also intracranial dilatation); temporal arteritis | Decrease T1 to T4 sympathetic nerves; improve lymphaticovenous drainage; calm CN X to decrease vomiting/ nausea |
| Vertebral artery and/or immediate branches | dissection/thrombus | Wallenberg syndrome; locked-in syndrome (posterior headache) | **OMT contraindicated** |

| *Structure involved* | *Stimulation* | *Headache syndrome* | *OPP/OMT approach* |
|---|---|---|---|
| Occipital nerve | C1 to C2 joint pathology (cervical rheumatoid or osteoarthritis, fracture or carcinoma) | occipital neuralgia | OMT to restore motion and decrease somatic afferent stimuli from occipitoatlantal to C3 (which have connections to greater and lesser occipital nerves and CN V, CN IX and CN X) |
| *Intracranial* | | | |
| Blood vessels (and adjacent dura) | dilatation | hypoxia; hypoglycemia; hyperthermia; hyperthyroidism; | **OMT adjunctive** or primary; decrease T1 to T4 sympathetic |

| | | | |
|---|---|---|---|
| | | hangover; severe hypertension; posttraumatic migraine | hyperactivity |
| Blood vessels (and adjacent dura) | inflammation | meningitis; subarachnoid hemorrhage | **relative contraindication to OMT** |
| Middle meningeal artery and environs at restricted sphenosquamous pivot | impaired or altered temporosphenoidal motion; vascular irritation; autonomic | post-traumatic middle meningeal migraine | restore motion at sphenosquamous pivot; balance membranous/dural tension |
| Dura (and adjacent blood vessels) | cranial or spinal dural irritiation; pressure on cranial dura; dural strain (traction/ displacement) from cranium to sacrum | dural strain headaches; brain tumor; hematoma; abscess; hydrocephalus; postlumbar puncture headaches; posterior cranial fossa (CN X/ C2 distribution headache); middle or anterior cranial fossae (CN V distribution headache) | **OMT adjunctive** or primary; remove cranial restricted motion; balance membranous/dural tension; decrease T1 to T4 sympathetic hyperactivity |

OPP, osteopathic principles and practices; OMT, osteopathic manipulative treatment

and Simons[74] and others[54] noted the major role of postural imbalance and sacroiliac dysfunction in the precipitation and perpetuation of pain and dysfunction in the lumbopelvic region.

The value of diagnosing lumbar and pelvic (sacral, innominate and pubic) somatic dysfunction is well established in the literature. Greenman performed a study of 183 consecutive patients presenting with disabling low back pain (average duration 30.7 months). Three or more of what he called the 'Dirty Half Dozen'[113] somatic dysfunctions were found in

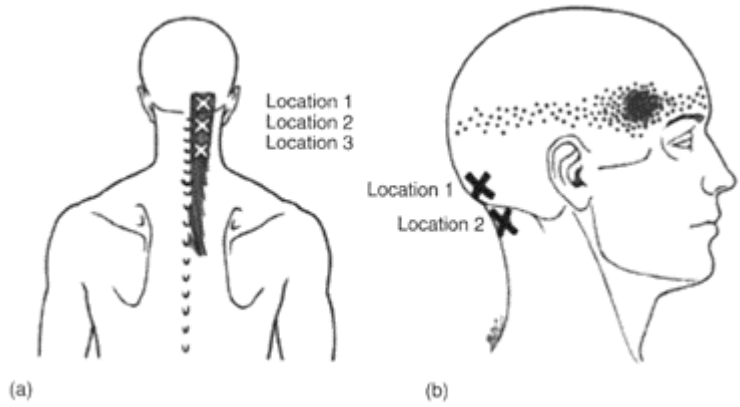


**Figure 8** Semispinalis capitis myofascial trigger points and upper cervical (C0 and C1) somatic dysfunction are found routinely at locations 1 and 2 resulting in the non-throbbing headache pattern shown in Figure 8b. Middle semispinalis capitis at location 3 results in ipsilateral posterior parietal headache. TrPs in location 2 can result in greater occipital nerve entrapment. Reproduced with permission from reference 51

50% of this population. Correction of the dysfunction using integrated rehabilitative approaches that specifically included OMT resulted in the return to work and restoration of normal activities of daily living for 75% of these patients.

The osteopathic palpatory examination approach to a patient presenting with the symptom of 'low back pain' expands the physician's differential diagnoses and treatment options. It includes the early diagnosis and treatment of identified somatic dysfunctions with emphasis on addressing certain perpetuating factors, including even minor postural asymmetries and muscle imbalances.

The body of evidence[114] suggests that, regardless of who delivers the manual technique (chiropractor, therapist, osteopath, osteopathic physician, physician-in-training, or manual medicine specialist), there is a probable short-term benefit in an earlier return to activity, adequate patient satisfaction and even reduction of NSAID usage when patients with acute low back pain (especially uncomplicated, acute low back pain) receive generic manual treatment approaches. However, inadequate numbers of quality

studies prevent the use of meta-analysis to make conclusions concerning the efficacy of spinal manipulation for chronic low back pain or to comment on long-term effects of this form of treatment in general.

While many studies have measured the impact of a 'manipulative technique' protocol, few studies have been conducted specifically to study the osteopathic approach to low back pain. Even the largest of the osteopathic studies in the treatment of low back pain was limited to an OMT-added group without any protocol to allow for treatment of underlying postural or other biomechanical abnormalities that might have co-existed. The outcomes of OMT in this randomized, controlled study published in the *New England Journal of Medicine*[115] showed that the OMT group accomplished the same outcomes as the traditional care group, but with the use of less medication and physical therapy modalities. Less NSAID usage was interpreted to have the potential for less cost and less likelihood of complications secondary to NSAID use.

Finally, few controlled studies have been conducted to examine the cost of an osteopathic approach to treatment of patients with low back pain. As noted above, the article[115] postulated less expense, but this is supposition only. Retrospective analyses of costs for Worker's Compensation claims in several states (data compiled by Labor and Industry computers in Florida (FCER, 1988, Arlington, Virginia) and Colorado (Tillinghast, 1993, Denver, Colorado) documented less expense, but these did not allow separating out which of

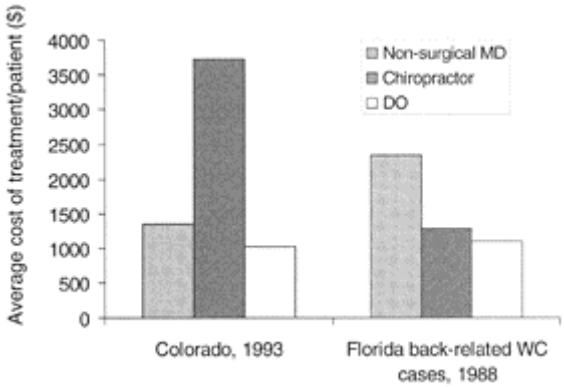


**Figure 9** Workers' compensation (WC) data, showing cost-efficacy of the osteopathic approach. Data compiled by Labor and Industry computers in Florida and Colorado

these (or other) factors were involved, nor did the study distinguish between those osteopathic cases that received OMT and those that did not. However, it was demonstrated that the osteopathic approach to low back pain (and to all other Worker's Compensation injuries in each region analyzed) was the least expensive, i.e. more cost-

effective, than any other management approach, including care by nonmanipulative physicians, surgical physicians, physical therapists and chiropractors (Figure 9).

### *Neurodegenerative disorders*

Integrating OMT protocols, ostensibly to assist homeostatic mechanisms and/or to maximize function within their existing compromised neuromuscular structures, would seem to be fruitless in patients with a chronic progressive neurodegenerative disease. Recent studies, however, have indicated that improvement in posture, gait, balance, expended energy to accomplish activities of daily living, and so on, may permit an improvement in the quality of life that would otherwise not be available.

Currently under study is the effect of OMT in subjects with Parkinson disease. The current study builds upon pilot data from the New York College of Osteopathic Medicine in which a single OMT intervention created statistically significant improvement in various gait parameters[116,117] (Figure 10), including length of stride, height of raising the foot and ankle, linear velocities of various aspects of the extremities and head postural angle.

In subjects with multiple sclerosis, an osteopathic protocol, consisting of OMT and progressive maximal effort exercise, resulted in dramatic increases in strength that lasted for the several months after the subjects had discontinued the exercise protocol[118]. Studies are currently underway to look at the exercise protocol in isolation (without OMT) and in conjunction with different physical modalities.

## Osteopathic considerations in internal medicine disorders

While taught as a routine component of every encounter, a structural examination that seeks somatic clues to aid in differential diagnosis of symptoms can be valuable. For this reason, the AOA requires an osteopathic structural examination for all osteopathic hospital admissions in AOA-accredited hospitals. The documentation can be narrative or can incorporate diagrammatic elements, as shown in Figure 11.

The value of assessing somatic dysfunction in differential diagnostic issues can be significant. A wealth of clinical evidence, including a 5-year double-blind study of 5000 hospitalized patients[119], suggests that the differential diagnosis of palpatory findings in the thoracolumbar spine should include secondary somatic dysfunction of segmentally related visceral disorders, and those in the craniocervical region should include secondary somatic dysfunction from sinus, respiratory, cardiac and gastrointestinal disorders[90,120].

Several mechanisms have been proposed and/or documented to explain various aspects of the tissue texture abnormalities and other somatic, visceral, vascular, lymphatic, immune, and neural responses seen in primary and secondary somatic dysfunction[121–124]. As previously mentioned, nociceptive levels of somatic dysfunction, especially in severe and prolonged somatic dysfunction, create segmental

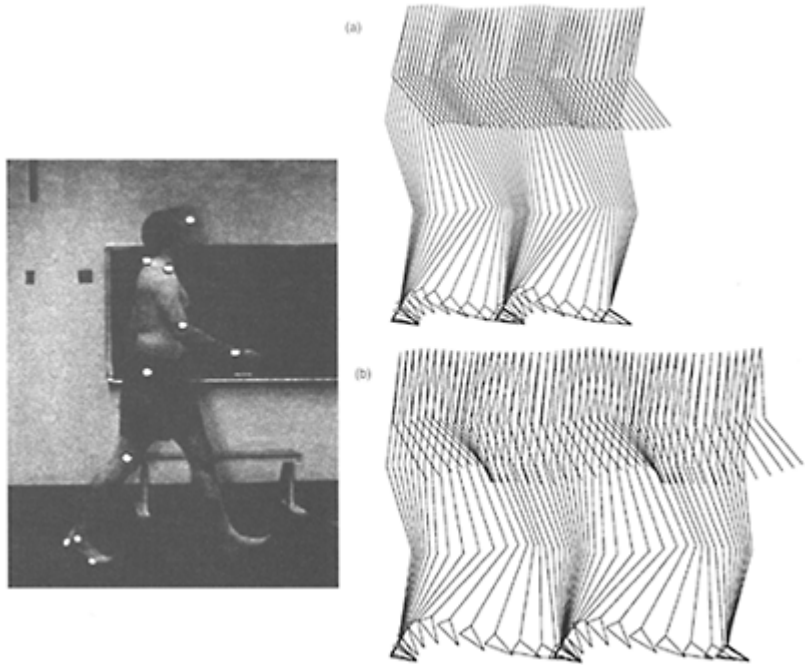


**Figure 10** Pre- (a) and post- (b) osteopathic manipulative treatment in patients with Parkinson's disease

spinal facilitation and significant peripheral pathophysiological change[47,125] resulting in significant tissue texture abnormalities. Similarly, many primary visceral afferent fibers affecting the spinal cord have the characteristics of nociceptive fibers. They produce neuropeptides such as substance-P and calcitonin gene-related polypeptide and respond to nociceptive stimuli. Some are even capable of eliciting a neurogenic inflammatory response in the surrounding tissue[126,127]. Thus, both somatic and visceral conditions are capable of creating musculoskeletal clues palpable as somatic dysfunction.

From a diagnostic perspective, palpation for somatic dysfunction in patients with visceral disorders is one of the hallmarks of the osteopathic approach[13]. Relatively consistent palpatory findings are present, because visceral disorders stimulate afferents that, in turn, result in progressive and distinctive findings of secondary somatic dysfunction according to the autonomic innervations and sidedness of the involved viscus (Figure 12). Progression in the early visceral phase tends to be vague, poorly localized and midline over the appropriate collateral ganglion. As the visceral condition progresses, somatic clues are added in the form of paraspinal tissue texture changes (more so than restricted motion), Chapman's intercostal reflexes and rib somatic dysfunction. By the time that the visceral problem ruptures or irritates adjacent visceral pleura/peritoneum, the peritoneocutaneous reflex localizes over

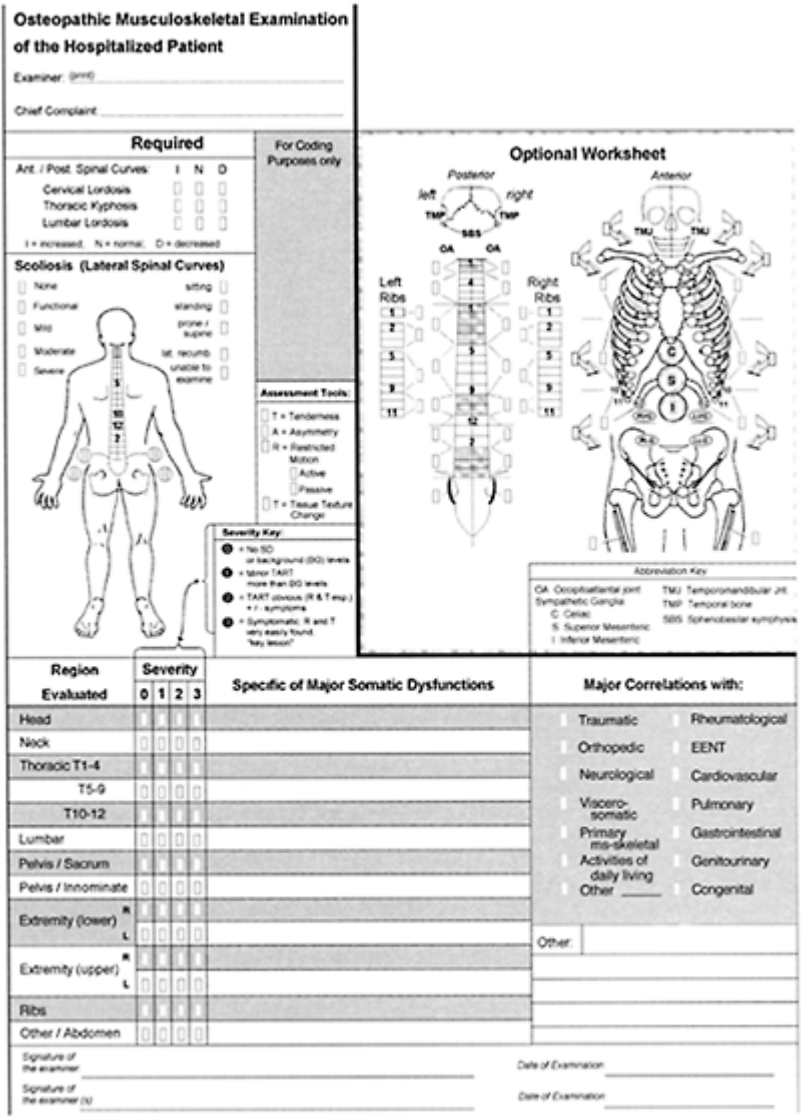


**Figure 11** Standard in-patient osteopathic examination form

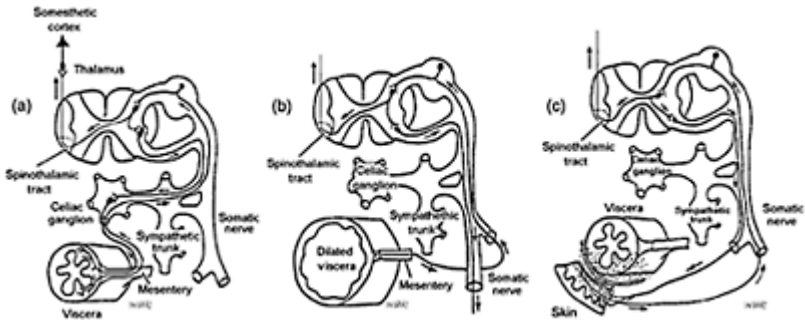


**Figure 12 (a–c**) Progression of pain and palpatory reflex findings in visceral disorders. (a) visceral reflex; (b) viscerosomatic reflex; (c) peritoneocutaneous reflex. Reproduced with permission from reference 90

viscus-specific sites (as in the appendix and its McBurney's point). This progression of pain and somatic findings in visceral disturbances have been extensively documented by osteopathic physicians in the USA[90,91], by surgeons at the Mayo Clinic Foundation[128], and by pain management specialists[129,130] world wide.

From a treatment perspective, primary somatic dysfunction typically responds well to the various management strategies[51,131] as previously discussed, whereas somatic dysfunction secondary to visceral disorders responds variably and often recurs[90,132] when addressed by these approaches alone. That is not to say that there is no effect. Paterson provides a synopsis of 'bizarre ENT symptoms' resulting from cervical dysfunction and notes that, in the absence of contraindications, manipulation is the treatment of choice[133]. Maigne indicates that, when cervical somatic dysfunction is eliminated with manipulation, precipitating visceral factors that are still present will no longer trigger the referred headaches[134]. Travell and Simons noted that non-responsive gastric ulcers previously responsive to medication became nonresponsive in the presence of myofascial trigger points in the anterior thoracoabdominal region and did not respond to medication again until this somatic dysfunction was removed[135].

In isolation, palpation does not provide enough diagnostic information for full evaluation of a patient's complaint; a physician's diagnostic capability with concomitant palpatory skills to investigate and/or co-manage both visceral and somatic conditions are required for formulation of a complete differential diagnosis and treatment plan.

The segmental facilitation model has held up well in the correlations seen between the level of spinal somatic dysfunction and the autonomic innervation level associated with a given organ that is dysfunctional or diseased (refer back to Figure 3). Furthermore, recent research is beginning to document the value of the empirically derived system of Chapman's reflexes (Figure 1). To date, the sensitivity and specificities of the points tested have averaged 80% and their use in a blinded series of gynecological problems

resulted in 80% sensitivity for the presence of ovarian disease and a 95% accuracy for identifying the side of involvement[136].

The integration of palpation data in the differential diagnosis of systemic disorders and suggestions for the use of OMT for removing somatic dysfunction to augment homeostatic mechanisms in the neural, vascular and lymphatic areas of a patient can be found in the text *Osteopathic Considerations in Systemic Dysfunction*[90].

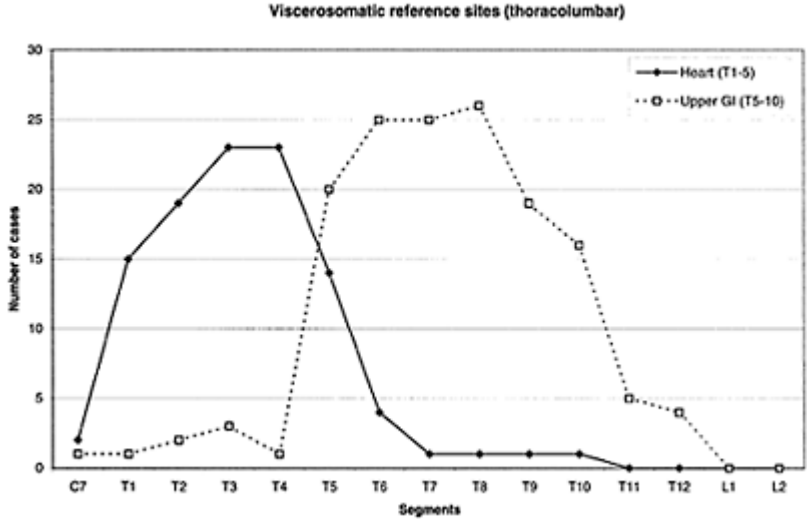


**Figure 13** Comparison of somatic dysfunction locations in patients with cardiac and gastrointestinal diagnoses

Palpation to identify somatic dysfunction in hospitalized patients as an aid to making a differential diagnosis has maintained its prioritization. However, as diagnosis related group (DRG)-regulated hospital stays have both decreased in duration and increased in the severity of illness, the use of in-hospital OMT has dropped significantly. Today, most osteopathically delivered OMT is in the out-patient setting and studies indicate that the coding for that procedure is primarily associated with neuromusculoskeletal (somatic) diagnoses. Nonetheless, research, currently underway, suggests that intervention with OMT in certain categories of hospitalized care may be effective in decreasing the need for postoperative pain medications, providing earlier post-surgical ambulation for patients who have undergone orthopedic lower extremity procedures[137] and decreasing length of stays in general. Perhaps this is the result of decreasing side-effects of the alternative use of certain medications or reducing the need for intravenous catheters and intravenous medication[138].

*Diagnosis and adjunctive treatment of viscerosomatic disorders*

From the osteopathic perspective, failure to consider somatic dysfunction limits the differential diagnosis and overlooks an important underlying pathophysiological process that may limit optimum health and performance or play a role in a patient's complaints. The presence of moderate to severe somatic dysfunction in particular spinal patterns correlates with and thereby augments the differential diagnosis of a wide range of visceral conditions[90,128,139]. Indeed, irritationof upper thoracic spinal joint receptors simultaneously evokes numerous reflex alterations, including paravertebral muscle spasm and alterations in endocrine, respiratory and cardiovascular functions[140].

The cardiovascular system is perhaps the most documented system in which the clinical recognition of somatic dysfunction in health and 'dis-ease' has been demonstrated. Specific palpatory findings of upper thoracic somatic dysfunction (especially affecting left upper thoracic paraspinal tissues) were reported in the *British Medical Journal* as being consistently found in myocardial infarction[141]. Similarly, Travell and Simons' text reports the palpatory finding of trigger points in the pectoralis major muscles in 61% of 72 patients with cardiac disease[51]. These palpatory findings of somatic dysfunction have a completely different pattern of distribution from the secondary somatic dysfunction associated with patients with gastrointestinal problems[139] (Figure 13).

Conversely, evidence of neurologically mediated somatovisceral reflexes is cited in Travell and Simons' text[51]. For example, removal of primary myofascial somatic dysfunction in the pectoralis major muscle 011 the right in patients with some forms of supraventricular tachyarrhythmia 'promptly restores normal sinus rhythm…and also can eliminate recurrences of the paroxysmal arrhythmia… for a long period of time'[51]. Other somatovisceral reflexes are implicated in patients with systemic symptoms ranging from asthma to duodenal ulcers to dysmenorrhea, and those with functional gastrointestinal disorders[74], including irritable bowel syndrome[90].

In response to a variety of stimuli, homeostatic functions are defensively altered through a series of complex feedback loops that monitor conditions in the peripheral tissues and make local and systemic adjustments as needed. Excessive driving stimuli or dysfunction of the feedback circuits themselves results in decreased compensatory reserve, 'dis-*ease*' and increased susceptibility to disease. The three primary driving stimuli (stressors) initiating the cascade of chemical messengers first described in Selye's general adaptive response are emotional, somatic and visceral dysfunction[142]. These and other stressors create an allostatic load capable of disturbing the individual's normal homeostatic set point[143–145]. Their role and the role that somatic dysfunction specifically plays in disturbing homeostasis through reflex[30] and neuroendocrine-immune[124] responses to the inflammation, edema and nociceptive bio-chemical mediators[146] have been extensively documented[22,70].

## SUMMARY

While seeking health, the osteopathic approach to patient care is also designed to arrive at a differential diagnosis that considers both structural and functional problems. It builds much of the distinctive aspects of its approach on biopsychosocial, anatomical and pathophysiological models[147,148] and attempts to modify any and all stimuli (stressors) felt significantly to drive neurological and neuroendocrine responses. Somatic dysfunction has been shown in this chapter to be one of these stressors.

This chapter has also introduced OMT as a treatment modality for specifically treating somatic dysfunction as well as for modifying underlying nociceptive, postural imbalance and allostatic mechanisms and reflexes between somatic and visceral systems. The former use of OMT has documented effects in reducing pain and dysfunction. The integrated use of OMT is considered generally to assist in maintaining homeostasis while specifically addressing concomitant somatic dysfunction and reducing allostatic load. This latter perspective still separates OMT by osteopathic physicians in the USA from MDs who practice manual medicine[149], but hopefully this chapter has demonstrated the value of continued dialog and research collaboration.

For the neurologist, the implications of osteopathic diagnosis and treatment for enhancing differential diagnosis are significant. The evidence base surrounding the entity known as somatic dysfunction is still in development. Certainly removal of factors that modify or mimic a pathological neurological condition will aid in establishing more accurate diagnosis. Likewise, approaches designed to reduce pain and dysfunction and/or to diminish neuromusculoskeletal impediments to activities of daily living, balance, gait, or other movements should be conscientiously investigated for their potential to enhance the care of patients with various neurological diagnoses.

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# 5
# Massage therapy

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*Complementary Therapies in Neurology: An Evidence-Based Approach*
Edited by Barry S.Oken
ISBN 1-84214-200-3 

## DEFINITION AND ORIGINS OF MASSAGE THERAPY

Massage therapy (therapeutic massage) is the manual manipulation of soft body tissues to enhance health and well-being[1]. Animal behavior indicates that the application of pressure, rubbing, vibration and joint movement are used instinctively to relieve pain or respond to injury[2]. Massage therapy is one of the oldest forms of medicine known to mankind, having been practiced worldwide since ancient times[1]. Archeologists have found prehistoric artifacts depicting massage for healing purposes. Fritz speculated that early massage was used for pain relief based on a theory of counter-irritation and utilized procedures such as scraping, cutting and burning of the skin[2]. Other massage techniques, including traction, rubbing the muscles and passively moving joints, have been documented in medical literature from ancient Egyptian, Persian, Greek and Roman civilizations. Ancient Greeks received friction, anointing and rubbing with sand before they took part in the Olympic games. The 'laying on of hands' for ritual, hygienic and therapeutic benefits has been recorded in Hebrew and Christian writings. The ancient Mayan people, the Incas, and other native people of the North and South American continents also used joint manipulation and massage. Massage has been a part of ayurveda, the 'art of life', in India for almost 3000 years. Chinese medical literature dating back to 2000 BC includes the words *anmo,* which means 'press-rub' and *tuina,* which means 'push-pull'[2,3].

Per Henrik Ling (1776–1839) is acknowledged for persistent experimentation with manual techniques and the development of Swedish massage. He proposed an integrated program consisting of active and passive movements (medical gymnastics) and massage for the treatment of disease. This system, which became known in the USA as the Swedish Movement Cure in the late 19th century, was based on the circulation of the blood and lymph.

In the USA, therapeutic massage was routinely used by physicians, nurses and physical therapists during the late 1800s and early 1900s. The research of Mary Putnam Jacobs and Victoria A. White, New York City medical doctors and professors of medicine in 1880, studied the benefits of massage and ice packs in the treatment of anemia. In more contemporary times, Dr Janet Travell has developed a respected body of

work in the field of myofascial pain and trigger points, and Bonnie Prudden popularized the trigger point work. Frances Tappen, a physical therapist, formalized the contributions of massage in her text, *Healing Massage Techniques*. Dr Ida Rolf's manual therapy system developed into 'rolfing'. Dr Delores Krieger has developed and popularized the energetic form of manual healing known as 'therapeutic touch' with nurses and other caregivers[2]. Despite this activity, massage therapy was virtually abandoned as a part of medicine by the time of World War II[1]. However, in the past 25 years, interest in therapeutic massage has grown dramatically in the USA. In 1997, trained massage therapists provided an estimated 114 million 1-hour massage sessions per year[4]. More than twice as many adult Americans reported receiving one or more massages from a massage therapist in the past year (18%) as did in 1997 (8%). In 2002, 28% of Americans said they had had a massage in the past 5 years—an increase of 11 percentage points since 1997[5].

## CONTEMPORARY PRACTICE

Contemporary massage practice includes a variety of theoretical orientations or approaches to working with the client, all of which share the underlying philosophy of helping the body to heal itself[1]. These approaches include relaxation massage, deep tissue techniques, movement re-education, subtle energy techniques and various forms of Asian bodywork. Within each approach, there may be numerous specific styles of massage (e.g. Eastern body therapies include shiatsu, Thai and tuina, among others) and within each style, one or more techniques may be used (e.g. tuina includes kneading, rolling and cupping). Specific techniques may be included in different styles of massage (for example, kneading can be used as part of Swedish, tuina and some deep tissue styles). In order to augment the effect of hands-on techniques, massage therapists may recommend various types of self-care such as stretching and strengthening exercises, exercises designed to increase body awareness, and the drinking of sufficient water[6].

## COMMON FORMS OF MASSAGE

Distinctions in clinical applications originate in the practitioner's theoretical approach to bodywork. Some primary approaches include relaxation or Swedish massage, deep tissue techniques, movement re-education, subtle energy techniques and Eastern approaches to bodywork.

Swedish massage is used primarily to relax the patient. Five basic strokes are employed: effleurage (gliding), petrissage (kneading and lifting), friction (moving the tissue layers underneath the skin), vibration and percussion. In the USA, the most widely taught and practiced style of relaxation massage is Swedish[1,7]

Deep tissue massage involves deeper manipulation of the muscle or surrounding fascia and to more specifically address pain and restricted movement[7]. Deep tissue techniques may include the same strokes that Swedish practitioners use, albeit with the application of greater pressure (usually but not always) as well as other strokes[1]. Some of the better

known styles of deep tissue work are myofascial trigger point therapy, Myofascial Release™, Structural Integration or Rolfing™ and Hellerwork™[8,9].

Movement re-education uses movement to enhance body awareness and movement for the patient[7]. Some styles of movement reeducation emphasize active exercises (e.g. the Alexander Technique™) to teach healthier ways of moving. Others emphasize tablework in which the practitioner induces, assists or resists movement for a patient (e.g. Proprioceptive Neuromuscular Facilitation™, positional release, passive and active assisted or resisted exercise and stretch). A third group of movement therapies offers a combination of tablework and exercises (e.g. Trager™ and Feldenkrais™)[8,9].

Subtle energy techniques (also called energy work or body-mind therapies) attempt to assist the flow of energy in the body through either very light touch or holding of the hands just above the skin[7]. These include Reiki, Polarity, Therapeutic Touch and craniosacral techniques. Craniosacral techniques are based on a Western osteopathic understanding of the body with particular emphasis on the skull and sacrum, whereas other energy therapies postulate non-physiological theories based on an 'energy body' that is believed to coexist with the physical body[10].

Several highly developed massage traditions derive from cultures of Eastern countries[1] such as China, Japan and India. Chinese massage techniques, which focus on treating imbalances in the body's energy or chi, include acupressure, amma and tuina. These systems theorize vital body energy flowing through meridians or channels which, so far, do not correspond with any Western anatomically described structure. Shiatsu ('finger pressure'), a type of acupressure, is the major form of Japanese massage. Ayurvedic massage, the most recognized Indian technique, utilizes special oils and hand strokes to restore energy flow through vital centers of the body called 'chakras'[8,9].

## STATUS OF THE PROFESSION

### Use

An estimated 13.5 million Americans visited massage therapists in 1997 with each user averaging eight visits[4]. Musculoskeletal problems, especially back and neck pain, as well as relaxation and wellness were the most common reasons for visits to massage therapists[11].

Providers with other credentials may also offer massage. For instance, soft tissue manipulation may be included in chiropractic care. Osteopathic physicians may incorporate massage into their medical practices. Swedish massage technique (relaxation massage) is used in the standard 'back rub' taught in nursing schools. Physical therapists and physical therapy assistants may use Swedish, trigger point, myofascial and other massage techniques. Podiatrists may utilize foot massage and some dentists are incorporating intraoral massage. Mechanical massage devices are used for specific medical indications, such as to prevent decubitus ulcer or thrombosis of the veins of the lower extremities during convalescent care and to prevent or reduce postmastectomy lymphedema[3]. Caregivers and family members may also be trained by massage therapists in the use of specific massage or relaxation routines for preterm infants, behavioral disorders related to dementia, or other rehabilitative purposes.

## Education

The number of training programs in massage has increased dramatically in the past decade, in part because of an increasing public demand for complementary approaches to health care. Currently, there are more than 800 massage training programs in the USA; education requirements for massage therapists vary from state to state[12]. Depending on the state and the individual institution, massage training programs may lead to a certificate, diploma or associate's degree. At least one school in California (International Professional School of Bodywork) has offered a master's degree in bodywork.

Massage therapy schools teach communications skills, Eastern and Western bodywork modalities and philosophies, anatomy, physiology, pathology, kinesiology, business practices, ethics and first aid/cardiopulmonary resuscitation. In addition to classroom studies, students participate in supervised clinical internships. Some schools and colleges offer or require externships as well, which are typically conducted in hospitals, hospices, assisted care organizations, athletic departments and corporations[3].

Massage and bodywork schools throughout the country are accredited by several independent organizations including the Accrediting Commission of Career Schools and Colleges of Technology (ACCSCT), the Accrediting Council for Continuing Education and Training (ACCET), the Council on Occupational Education (COE) and the Commission on Massage Therapy Accreditation (COMTA).

## Credentialing

In 2001, the American Massage Therapy Association estimated[13] that there were between 260 000 and 290 000 massage therapists and massage students in the USA, about double the number estimated in 1996. Licensing requirements for massage therapists differ between states[12]. The National Certification Board for Therapeutic Massage and Bodywork (NCTMB) developed and administers the first national certification examination in therapeutic massage and bodywork, which is used by several states as a credentialing requirement. In 30 states plus the District of Columbia, massage therapists must be licensed, registered or certified by the state in order to practice[14]. In some states, including Massachusetts and California, regulations vary within the state (between townships, cities or counties). Most states require at least 500 hours of education to apply for permission to practice. Some states require ongoing continuing education credits in the field.

## Massage therapy referrals

A recent study[15] found that both patients and massage therapists believe that pain reduction is most affected by the therapist's accurate choice of technique. Another recent investigation[16] concluded that manual therapists (chiropractors) have different degrees of effectiveness even when utilizing the same technique. These studies suggest that specific training, experience and credentials contribute to a patient's successful experience with massage. Kalauokalani and colleagues[17] suggested that patients with positive expectations of massage are more likely to have a successful treatment experience (Figure 1). Referrals for professional members of the American Massage Therapy Association can be found through inquiries at

www.amtamassage.org/findamassage/locator.htm. Referrals for craniosacral, visceral and lymphatic therapists can be found through local massage schools or http://www.upledger.comorhttp://www.iahe.com.

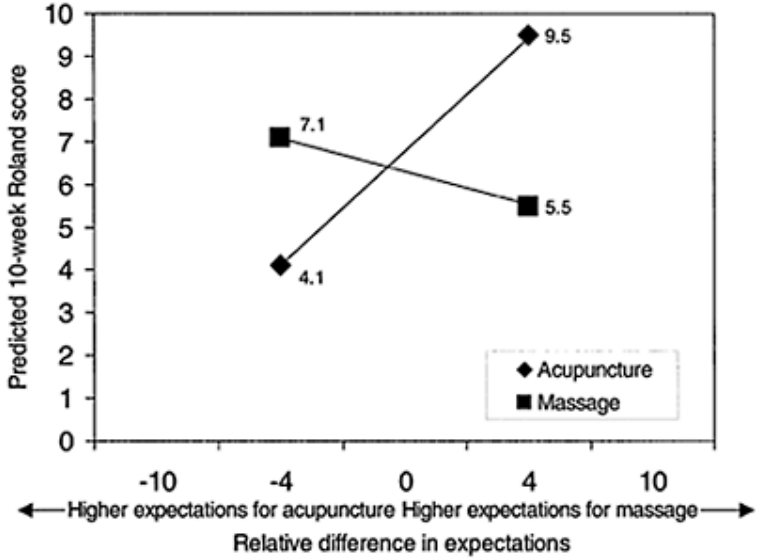


**Figure 1** Effect of patient's relative expectation of improvement from acupuncture versus massage on their low back pain (Roland score). Patients with greater initial expectation of improvement from massage were better if they received massage than if they received acupuncture. In contrast, patients with greater expectation of improvement from acupuncture did better with acupuncture. Plots are based on linear regression of individual patient data. Reproduced with permisssion from Kalauokalani D, *et al.* Lessons from a trial of accupuncture and massage for low back pain: patient expectations and treatment effects. *Spine* 2001; 26:1418–24[17]

Massage therapists must possess good interpersonal skills along with sensitivity and empathy. Furthermore, massage therapists with minimal training should not treat patient until they have received specialized training[3]. Local massage schools keep records of graduates and their areas of specialty. In addition, complementary and alternative medicine (CAM) centers, biomedical research institutions and teaching hospitals often have established collaborations with massage therapists who accept referral patients. All massage therapists and practitioners must adhere to a code of ethics and the standards of practice and must respect the scope of practice[3].

## SCIENTIFIC RESEARCH ON MASSAGE

Research on massage therapy was first published in academic journals in the 1930s. In the past 30 years, some 200 articles on massage therapy, including about 100 clinical trials, have been published in journals that are included in MEDLINE[18]. These studies have focused on a variety of medical conditions and on physiological changes. However, despite the large number of studies, most are small, poorly designed, inadequately controlled and lacking in statistical analysis[18]. For example, many included co-interventions that made it impossible to evaluate the specific effects of massage, while others evaluated massage delivered by individuals who were not fully trained massage therapists following treatment protocols that did not reflect common (or adequate) massage practice. Meta-analyses across studies are difficult to achieve and interpret because of wide variations in modalities used, individual techniques employed, dosage (length and frequency of sessions) and variations in outcomes measured. Since results tend to be obtained immediately post-treatment, there is little or no systematic inquiry into the duration of effects. Massage research has tended to be underfunded, with a result that studies have not been conducted over a long period of time and follow-up data are scant[19]. Thus, despite the growing popularity of massage in the USA, there have been few well-designed controlled clinical trials evaluating the effectiveness of massage.

### Physiological effects

Research suggests that massage has psychological benefits as well as a range of beneficial effects on a variety of body systems, including the musculoskeletal, circulatory-lymphatic and nervous systems[1]. Specific physiological changes that have been documented include improved connective tissue pliability and mobility, increased joint mobility, improved circulation, enhanced immune system function and reduction in stress hormones[1]. Massage is thought to help restore pliability in connective tissues damaged by trauma or disease by softening fibrous adhesions and encouraging new tissues to be established in more appropriate ways[20]. Massage appears to increase joint motion by relaxing muscles and other soft tissues surrounding the joint. For example, Nordschow and Bierman[21] found that healthy adults who received one massage focused on their back and legs were subsequently able to move their fingertips 1.35 inches closer to the floor as a result of their increased flexibility.

### *Circulatory effects*

Changes in the circulatory system reported after massage have been found in some studies, but not others. For example, Bell[22] and Hovind and Nielson[23], but not Shoemaker and colleagues[24] reported increased blood flow in the massaged region of the body. Decreased blood pressure and heart rate were reported by Fakouri and Jones[25] and Meek[26] but not Reed and Held[27]. Sabri and colleagues[28] found that deep vein thrombosis was reduced in 82% of massaged limbs compared with non-massaged limbs.

### *Immune effects*

A variety of changes in the immune system have been reported following massage, including increased lymphatic flow[29–31], increased concentration of salivary immunoglobulin A[32,33], increased numbers of natural killer (NK) cells, NK cytotoxicity, soluble CD8, the cytotoxic subset of CD8 cells in HIV-positive men[34] and increased numbers of lymphocyte markers and NK cells in women with breast cancer[35].

### *Hormonal and other chemical changes*

Animal studies have reported that touch (handling) increases the production of growth hormone and decreases the production of cortisol (stress hormone) in young rats (reviewed by Field[18]). Field's review of human studies[18] found that, compared with controls, preterm infants, cocaine-exposed infants and HIV-exposed infants all gained weight after receiving a series of three 15-min massages for 10 days. Additional documented physiological changes that occur in humans after specific types of massage include increased serotonin and dopamine levels[36], increased endorphin production[37], decreased blood glucose levels in diabetic children[38] and improved pulmonary function in asthmatic children[39]. In several studies, Field and colleagues have documented both psychological and physiological changes, including improved mood, decreased anxiety and reduced levels of stress hormones (cortisol, epinephrine, norepinephrine). These changes occurred after a series of eight to ten bi-weekly massages in people with a variety of conditions including posttraumatic stress in children[40], depression in children, adolescents and the elderly[41,42], eating disorders[43], chronic fatigue[44], and fibromyalgia[45].

### *Musculoskeletal effects*

Although massage is most often used to treat musculoskeletal conditions, there have been relatively few clinical trials evaluating massage for these problems. Massage and manipulation are widely used for osteoarthritis[46] and, although one literature review reported a favorable opinion, their effectiveness has not been investigated in controlled trials. An observational study suggested that aromatherapy massage increases the well-being of patients with rheumatoid arthritis (RA)[47] and, in another study, a decrease in self-reported and physician-assessed pain was noted in children with juvenile RA following a 30-day regimen of 15 min of daily massage administered by their parents[48].

Two clinical trials of massage in fibromyalgia patients found that patients receiving a course of massage reported lower levels of pain at the end of the treatment period compared to controls[45,49] In a small study of massage for migraine headaches, those receiving massage reported fewer symptoms of distress, less pain and more headache-free days than those in a waiting-list control group[50] Furlan and colleagues[51] recently updated their Cochrane Collaboration systematic review of massage for the treatment of low back pain. This review included eight studies, four of which used 'massage' as a control condition for another treatment and were not designed to deliver a therapeutic massage treatment. Of the other studies, two[52,53] were given high methodological quality ratings using the Cochrane rating system. Both studies found that therapeutic massage was effective for reducing pain levels and improving functional status in patients with persistent back pain.

### *Digestive effects*

Based on four clinical controlled trials, Ernst[46] cautiously concluded that abdominal massage could be a promising treatment for constipa- tion.

## MASSAGE TREATMENT FOR NEUROLOGICAL SYMPTOMS

No single massage approach is clearly the most appropriate for treating neurological conditions. Numerous trademarked modalities (i.e. styles) have been developed and taught by individuals who use specialized language to describe their techniques. Some massage styles with different names may be essentially the same (e.g. Structural Integration and Rolfing™). Some commonly used styles of massage therapy, including deep tissue and neuromuscular therapy, are not consistently defined. For example, some practitioners consider neuromuscular therapy to be a synonym for deep tissue work. Other practitioners use the term 'deep tissue' to connote the application of Swedish massage strokes with strong pressure; others believe it is the application of acupressure; others believe it is the use of Myofascial Release™. In addition, the same technique included in multiple styles may be given different names (for example, deep effleurage, muscle sculpting and longitudinal friction are the same; skin rolling is a type of petrissage).

Consistent terminology that clearly describes what is being done to the body (e.g. longitudinal friction, fascial stretching) helps facilitate more accurate analysis of the efficacy of massage techniques used with patients. Therefore, to the degree that is possible, the massage techniques used in the research study are specified when presenting the scientific evidence in regards to neurological conditions.

### Specific neurological symptoms and their treatment

#### *Pain*

Massage therapists commonly work with patients who present with chronic pain, and pain and stress reduction are major motivators cited by patients seeking massage. Of

those Americans who had received a massage in the previous 5 years, 35% cited medical reasons: to reduce muscle soreness, stiffness and spasm (10%), to reduce or manage pain (10%) and for injury recovery and rehabilitation (8%). An additional 25% cited relaxation (15%) and stress reduction (10%) as primary motivating factors[5]. Because some acknowledged causes of pain may be neuromuscular, myofascial or postural problems, specially designed massage modalities may be useful and even necessary in the treatment of chronic pain. Deep tissue[54] (including myofascial and neuromuscular styles), neuromuscular[55], cranial-sacral therapies[10], acupressure[56] and the use of active or passive stretching and exercise[57,58] have been suggested as useful strategies for the management of chronic pain. A Consumer Reports survey[54] rated deep tissue massage significantly more effective than standard physical therapy or prescription drugs for back pain and fibromyalgia and rated complementary approaches comparable to standard medical practice for neck pain. Massage therapists in the USA typically treat chronic pain in hourlong sessions utilizing a combination of styles, based on the clinician's training and experience and the individual needs of the patient[12].

In the treatment of chronic spinal pain, manual techniques are used to identify painproducing structures and reduce the pain with the aim of blocking the nociceptors[59].

Furlan and colleagues[51] qualitatively analyzed nine publications reporting on eight randomized trials because of heterogeneity of population, comparison groups, massage technique, timing and outcome measures in a Cochrane Collaboration systematic review of the effectiveness of massage therapy for back pain. One study showed that massage was superior to an inert treatment (sham laser), especially if given in combination with exercises and education. In the other seven studies, massage was found to be superior to relaxation therapy, acupuncture and self-care education, equal to corsets and exercises and inferior to manipulation and transcutaneous electrical nerve stimulation (TENS). The beneficial effects of massage lasted at least 1 year after the end of the treatment. One study comparing two different massage styles concluded that acupressure massage was superior to relaxation massage. Preyde[53] found that a group receiving comprehensive massage improved to a statistically significant degree in increased function ($p<0.001$) and less intense pain ($p=0.006$) over a group receiving soft tissue manipulation, and that both improved more than a sham laser group. In a subanalysis of data derived from a randomized controlled trial (RCT) that demonstrated massage efficacy over acupuncture and self-care for back pain[52], Kalauokalani and colleagues[17] observed that, after adjustment for baseline characteristics, 86% of participants with higher expectations for the treatment they received had improved function, as compared with 68% of those with lower expectations ($p=0.01$), suggesting that positive patient expectations about massage may greatly enhance the efficacy of treatment.

In a critical review of the effectiveness of massage therapy for a variety of conditions, Ernst and Fialka[60] failed to identify any published studies designed to evaluate the effect of massage on neck pain. Since that time, Irnich and colleagues[61] have published a study comparing relaxation massage (performed by physiotherapists) to sham laser acupuncture and to real needle acupuncture as treatments for neck pain. After a maximum of five 30-min sessions over 3 weeks, patients receiving acupuncture or sham acupuncture showed a significantly greater improvement in motionrelated pain than those receiving massage. However, the massage given in this study does not resemble what would happen in conventional practice in the USA, where massage therapy sessions would be longer, be

provided by a licensed massage therapist and include a wider range of massage techniques as well as self-care recommendations.

### *Anxiety and depression*

Several randomized controlled trials suggest positive effects of massage for anxiety, for instance in depressed adolescent mothers[62], women with premenstrual syndrome[63], multiple sclerosis patients[64], migraine sufferers[50] and elderly institutionalized patients[65]. Twenty-eight neonates born to HIV-positive mothers were randomized to receive either 15-min massages daily for 10 days or no intervention. The clinical score to evaluate the infants' development showed better outcomes for the neonates treated with massage[66]. Massage (once daily for 5 days) was related to improvements in depression and anxiety, night-time sleep and cortisol levels in an RCT ($n$=72) involving children and adolescent in-patients with depression and adjustment disorder[41]. Fritz[2] claimed that massage of the soft tissues (muscles and connective tissue) and movement re-education may have the effect of increasing the availability of neurotransmitters such as norepinephrine, dopamine or serotonin and, thus might play a part in the comprehensive care program for depression. She also recommended massage and movement re-education as part of a comprehensive management strategy dealing with anxiety symptoms.

Historically, massage has been used for depression in the 19th century, along with drugs such as ferrous iodide, arsenic, ergot, strophantin and cinchona, before the use of antidepressants (which have been known for only approximately 30 years[67]). Massage for the feet, back and neck has been applied to German schizophrenics for relaxation and to increase their awareness of their own bodily limits[68], and in Russian children at risk for schizophrenia, to correct locomotor function[69].

### *Fatigue*

Patients undergoing bone marrow transplantation[70] who received 20-min sessions of shoulder, neck, head and facial massage demonstrated significantly larger reductions in fatigue, distress, nausea and state anxiety than the standard treatment group. In another study, caregivers of patients undergoing bone marrow transplantation[71] treated with massage therapy showed significant declines in general fatigue, reduced motivation fatigue and emotional fatigue, as well as in anxiety scores and depression, as opposed to caregivers treated with Healing Touch or no treatment. Twins with chronic fatigue syndrome (CFS) are more likely to use massage as well as a host of other alternative treatments (homeopathy, megavitamins, energy healing, biofeedback, relaxation/meditation and others) than their non-CFS twins[72]. In a pre-post test design, with comparisons within and across groups, 100 hospital employees who experienced massage therapy, music relaxation with visual imagery, muscle relaxation and social support group sessions reported decreases in fatigue, confusion, anxiety and depression as well as increased vigor following sessions.

*Headaches and migraines*

Compared with baseline values, a marked reduction in headache quantity within the first

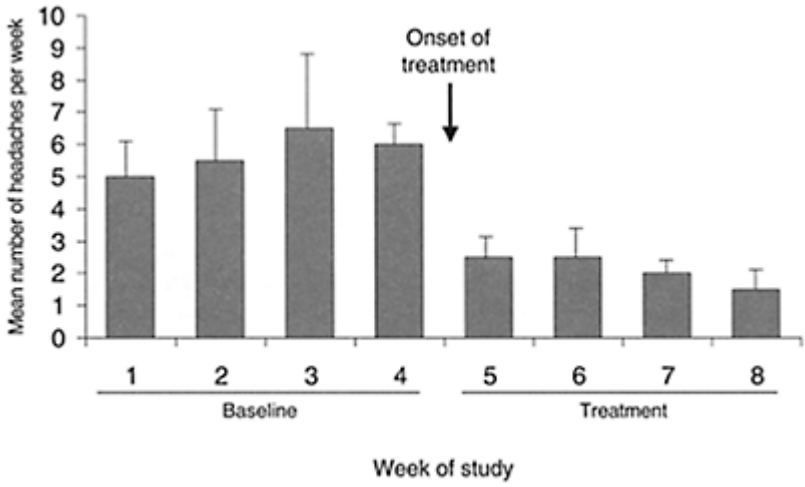


**Figure 2** Effect of muscle-specific massage treatments given two times per week for 4 weeks on non-migraine headaches in a small prospective trial. The control condition in this study was taken as a series of baseline assessments prior to the initiation of the massage intervention. Reproduced with permission from Quinn D, *et al.* Massage therapy and frequency of chronic tension headaches. *Am J Pub Health* 2002; 92:1657–61[73]

week of treatment was reported by four subjects who completed eight muscle-specific massage treatments (twice per week for 4 weeks) (Figure 2)[73]. Patients were non-migraine chronic headache sufferers. The reduction in headache frequency continued for the remainder of the study ($p$=0.009). The duration of headaches tended to decrease during the massage treatment period ($p$=0.058). Headache intensity was unaffected by massage ($p$=0.19). In an exploratory study of 220 patients with migraine or tension headache, 81% of patients reported that they were helped by massage treatments or cured of their headache problems at the 3-month follow-up[74]. Massage therapists themselves recommend massage for headache and migraines[75]. Australian physiotherapists report the

use of massage techniques including postural education (30.2%), soft tissue massage (35.6%), muscle stretches (29.2%), passive movements (17.3%) and muscle retraining (16.8%)[76]. Some researchers suggest that non-drug therapies (such as relaxation, sleep, massage, ice packs and biofeedback) should be tried first to treat migraine in women who are pregnant[77]. Patients themselves commonly self-administer massage, with the most often applied techniques being compression (114 out of 382 maneuvers, 30%), cold applications (27%), massage (25%) and heat (8%)[78]. Massage in the temples and nape was the most administered maneuver by tension headache patients (43%), while in migraine patients those without auras preferred cold (38%) and compression (36%), and those with aura preferred compression, mainly on the temple (44%). In another study of self-administered techniques[79], patients with migraines tended to perform more maneuvers (pressing, applying cold, trying to sleep, changing posture, sitting or reclining in bed, isolating themselves, using symptomatic medication, inducing vomiting, changing diet and becoming immobile during attacks) than patients with tension-type headaches who pre-dominantly used scalp massage. Patients who were randomly assigned to massage or acupuncture both showed a significant improvement in pain ratings; however, a greater effect was seen in migraine patients treated by massage[80]. In a prospective clinical controlled trial with 23 patients with post-traumatic headache pain, the mean pain index was significantly reduced to 43% for the group treated with two applications of specific manual therapy on the neck compared with those treated with cold packs[81]. At 5-week follow-up, the pain index was still lower in the manual therapy group, but the difference was not statistically significant. The pain index for all 19 patients who completed the study was significantly correlated to the use of analgesics as well as to the frequency of associated symptoms (e.g. dizziness, visual disturbances and ear symptoms). Puustjarvi and colleagues[82] administered ten sessions of upper body massage consisting of deep tissue techniques in addition to relaxation techniques and trigger point work to 21 female patients suffering from chronic tension headache. They found that the range of cervical movement increased in all directions, and the number of days with neck pain and visual analog scores (VAS) and other self-reported pain decreased significantly. There was a significant change in surface electromyogram (EMG) on the frontalis muscle, but not on the trapezius.

### *Fibromyalgia*

Sixty individuals who completed an online research questionnaire on fibromyalgia (FM) cited massage among the interventions tried more frequently and rated most effective, along with heat, support groups, walking, vitamins and literature[83]. While medications mainly focus on pain reduction, massage may reduce muscle tension and may be prescribed as an adjunct to other therapeutic interventions[84] such as TENS, biofeedback and trigger point injection. In a systematic review of commonly used CAM therapies for fibromyalgia, Berman and Swyers[85] found empirical research data to support the use of manipulative (including chiropractic and massage), mind-body (including biofeedback and hypnosis) and acupuncture therapies. For some patients with fibromyalgia, acupuncture can exacerbate symptoms, but that was not the case with massage. In 21 of 26 myofascial pain patients, a gradual decline in the increase in plasma myoglobin

concentration was found, parallel to a reduction in muscle tension and pain, after repeated massage treatment[86].

### *Bell's palsy*

Individual instructions for massage, facial exercise and muscle relaxation can support rehabilitation of patients with Bell's palsy and possibly support the production of pathological dyskinesia[87].

### *Central nervous system trauma*

Soft tissue and movement therapies can be an effective part of a supervised comprehensive care program. Massage can help manage secondary muscle tension resulting from the use of equipment such as wheelchairs, braces and crutches[2]. Specifically focused abdominal massage can help manage associated difficulties with bowel paralysis[46].

### *Support following surgery*

Massage therapists are taught that, before any work is done near the site of a surgical incision, the physician's approval must be obtained. In general, massage close to the surgical area can begin after all the stitches have been removed and all inflammation is gone. Direct work on a new scar is considered safe 8–12 weeks into the healing period[2].

A repeated measures ANOVA on a convenience sample of 20 patients aged between 66 and 97 years and recovering from hipfracture surgery showed that extended massage (60 seconds) on the sacral site resulted in a significant decrease in skin temperature as opposed to standard massage (30 seconds) received by a control group[88]. A Russian study[89] has suggested that the use of vibration massage at cardiovascular frequencies reduced the risk of pyoinflammatory complications in mandibular fractures. Patients undergoing bone marrow transplantation[70] who received 20-min sessions of shoulder, neck, head and facial massage demonstrated significantly larger reductions in fatigue, distress, nausea, and state anxiety than the standard treatment group. Vibratory massage (frequency of 8–11 tremors/s) produced a significant increase of mean tidal volume by 30% ($p$=0.008) and increased percutaneous oxygen saturation from 92 to 93.6% ($p$=0.04), along with significant decreases in central venous pressure by 11% ($p$=0.04) and pulmonary vessel resistance by 18.3% ($p$=0.001) in patients following heart or lung transplantation[90].

### *Neuropathies*

Soft tissue and movement therapies may provide short-term, symptomatic pain relief through shifts in neurotransmitters and stimulation of alternative nerve pathways, resulting in hyperstimulation analgesia. Depression and anxiety reduction that may result from massage may make coping with nerve pain somewhat easier for short periods[2].

### *Repetitive strain injuries*

Appropriate self-help strategies used at home may restore flexibility and strength with a minimum of medical intervention, but pain relief must be achieved before patients can be expected to follow through with rehabilitation efforts. Sheon[91] has suggested the use of massage, ice packs, non-steroidal anti-inflammatory drugs or topical pain-relief agents for pain relief, along with the importance of eliminating aggravating factors, such as improper posture and ergonomically unsound practices and habits. An Italian study of 13 out-patients (nine females, four males) who received massage and movement therapy involving the cervical spine and shoulder girdle, found that all patients were satisfied with the treatment outcome, and rest symptoms completely disappeared after treatment in all patients[92.]

### *Infectious disease*

Infectious processes are contraindicated for soft tissue interventions unless closely supervised by appropriate medical personnel[2]. The concern is that movement of the tissue may result in spreading the infection.

## Degenerative disorders

Sensory stimulation modalities such as rhythmic bodywork and movement may provide both calming and orienting influences[2].

### *Age-related dementia*

A systematic review of published research into strategies to alleviate behavioral disturbances in elderly persons with dementia found inconclusive evidence regarding massage[93]. Two studies published in that same year (1999) suggest that massage may indeed be of some benefit. Rowe and Alfred[94] reported that slowstroke back massage administered by caregivers decreased physical expressions of agitation such as pacing, wandering and resisting, and Kim and Buschmann[95] demonstrated lower anxiety immediately following expressive physical touch with verbalization (EPT-V) and fewer episodes of dysfunctional behavior. Previous studies[96,97] had found hand massage and therapeutic touch to be effective in producing a relaxation response in persons with dementia and a history of agitated behavior, and hand massage more effective in producing relaxation than therapeutic touch. Remington[98] reported a trend (albeit non-significant) towards reduced agitation in a similar population following massage.

### *Multiple sclerosis*

Massage and other forms of bodywork may help manage stress and the secondary muscle tension caused by the alteration of posture and the use of equipment such as wheelchairs, braces and crutches. Because therapeutic massage produces some stress, the intensity and duration of a massage intervention must be gauged so as not to aggravate the condition[2].

Huntley and Ernst's systematic review[99] of research studies utilizing CAM in multiple sclerosis, found evidence that massage improved depression, anxiety and self-esteem in patients and called for further investigations in the form of rigorous large-scale trials on massage. A controlled investigation of 20 patients with multiple sclerosis who received eight sessions of Feldenkrais bodywork, a specific type of movement re-education, found significant differences between those patients and others who received sham bodywork. Outcome measures were lowered stress and lowered anxiety with non-significant trends toward higher self-efficacy after both Feldenkrais and sham bodywork[100]. Among 16 respondents to a semistructured questionnaire, massage (along with physical therapy, counseling and nutrition) were the most frequently used 'alternative therapies'[101].

### *Parkinson's disease*

Because massage (as part of ayurveda—a holistic system of natural health care that originated in the ancient Vedic civilization of India) has been used for Parkinson's disease historically and because massage is one of the most often used forms of CAM therapy by patients with Parkinson's disease (along with botanicals and acupuncture), some researchers[102,103] suggest that it may have beneficial effects for patients and deserves further study. Others suggest that a more specific application of ice-massage to the oral region is probably effective for dysphagia in Parkinson's disease patients[104]. One German clinic's use of vibromassage (defined as 'swing-exbusar') for the loosening of muscular rigidity led to no 'sustained improvement'[105].

### *Cerebral palsy*

Seventy-five children received a combined treatment of acupressure, acupuncture and acupoint injection, and functional training to treat cerebral palsy. The 30 sick children who were treated 60 times were evaluated by appraising their before- and after-treatment IQ scores and measures of their physical exercise and social adaptability performance. The authors reported a positive improvement in physical capability and IQ[106].

### *Cerebrovascular accidents and strokes*

Soft tissue and movement therapies in a supervised setting may be supportive during rehabilitation after cerebrovascular accidents (CVA) or strokes. These methods may help manage discomfort caused by the functioning areas working harder to compensate for non-functioning areas. Stress management is an important part of the long-term management of these conditions. Because anticoagulants are often used to prevent further CVA or transient ischemic attacks, care needs to be taken with massage to avoid bruising during therapy. Careful attention needs to be paid to any symptom of thrombosis; the type of bodywork used should not place heavy pressure over vulnerable vessels, to avoid the possible movement of an embolism[2].

## CONTRAINDICATIONS AND ADVERSE EFFECTS OF MASSAGE

Common forms of massage (e.g. Swedish, deep especially when known contraindications to tissue and neuromuscular) carry very low risk, massage are observed[46,106]. For example, patients who have had recent strokes or heart attacks, communicable diseases, phlebitis, compromised immune systems, systemic edema or other systemic diseases or who cannot discern pain or who are excessively sensitive to touch should not receive massage. Massage therapists are trained not to massage anatomic sites containing some localized conditions such as skin injuries or burns. Ernst[46] stated that bone fractures and liver rupture were possible adverse effects of massage, but offered no evidence in support of that statement.

Massage may cause discomfort in sensitive areas, but therapists are trained to avoid techniques and pressure that patients find uncomfortable[107]. Deep massage can cause bruising or soreness that can persist for several days, but icing after a session will reduce the likelihood of these effects. Cherkin and colleagues[52] found that 13% of 78 patients receiving therapeutic back massage in a randomized trial reported increased pain, but no other adverse effects were elicited.

The most serious adverse effects reported after massage occurred after shiatsu massage was performed on the anterior neck. Tsuboi and Tsuboi[108] recorded an embolic accident after a ‘shiatsu’ treatment involving direct pressure to or around the extracranial carotid artery in an 80 year-old man who had recently been diagnosed with a transient ischemic attack. Two cases of carotid dissection, a well-described complication of head and neck trauma, were reported after using shiatsu-type massage tools (pressure bars)[109]. Mumm and colleagues[110] reported a case of probable traumatic zoster that might have resulted from direct trauma to the nerve or nerve roots during shiatsu massage. For these reasons, shiatsu massage and other types of pressure point massage on the anterior neck will be excluded from the massage protocol developed for this study. The only ‘massage-related’ death reported in the medical literature occurred when a woman who was using a roller-type electric massage device on her neck strangled herself accidentally because the cord became caught in her blouse[111].

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# 6
# Acupuncture and traditional Chinese medicine

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*Complementary Therapies in Neurology: An Evidence-Based Approach*
Edited by Barry S.Oken
ISBN 1-84214-200-3 

## INTRODUCTION

The history of traditional Chinese medicine and acupuncture can be traced back 2000 to 3000 years. In *Shi Jing* (Book of Poems), a collection of verse compiled in the 12th century BC, a number of herbs are mentioned. In *Shy Ji* (Records of Historian) written 104–91 BC, it is recounted that the technique of pulse taking and acupuncture was developed. Acupuncture is one of the treatment modalities within comprehensive traditional Chinese medicine. It has been practiced, now, for more than three millennia. Needles of flint, bamboo and bone from the Neolithic period suggest that acupuncture existed long before the discovery of metal. The 'Yellow Emperor's Classic of Internal Medicine' from the 4th century BC described the practice of puncturing the body for pain relief.

The acupuncture treatment is performed by inserting special hair-thin needles into the skin at specific sites, known as acupuncture points, for desired therapeutic and preventive purposes. Acupuncture can be effective in the treatment of mental as well as physical illnesses. The word 'acupuncture' is derived from the Latin words *acus*, 'needle' and *punctura*, 'a pricking'. The original term for acupuncture in Chinese is *Jin Jiao* which indicates the practice of 'acupuncture and moxibustion'. Moxibustion, the burning of moxa *(Artemisia vulgaris)* over the acupuncture points, can also be used for the treatment of various illnesses.

Acupuncture as a therapeutic intervention is now widely practiced in the USA. The National Institute of Health's (NIH) consensus development conference on acupuncture concluded that promising results supported the efficacy of acupuncture in adult postoperative and chemotherapy-related nausea and vomiting and in postoperative dental pain[1]. There were other situations, such as addiction, stroke rehabilitation, headache, menstrual cramps, tennis elbow, fibromyalgia, myofascial pain, osteoarthritis, low back pain, carpal tunnel syndrome and asthma, in which acupuncture may be useful as an adjunct or an acceptable alternative treatment, or one that might be included in a comprehensive management program. This chapter provides a practical and theoretical

understanding of traditional Chinese medicine and acupuncture, emphasizing its efficacy in various neurological diseases. The training and licensing requirements for acupuncturists and potential risks of acupuncture are also addressed.

## TRADITIONAL CHINESE MEDICINE

The use of traditional Chinese medicine and acupuncture can be traced back to Neolithic times. Archeological vestiges exist which testify to the antiquity of its practice, although the practice was first passed on as an oral tradition. *Huang Di Nei Jing* (The Yellow Emperor's Internal Classic), first compiled around 100 BC, described the practice of traditional Chinese medicine and acupuncture as puncturing the body for pain relief. This work was composed as a dialogue between the Yellow Emperor and his minister, Chi-Po. There are two depictions of sessions within the text, *Su Wen* (Common Questions) and *Ling Shu* (Direction of Soul/Spirit). Within traditional Chinese medicine, sharp distinctions are not made between the physical, psychological and synthetic. This contrasts with Western biomedical science, which tends to be reductionistic in its attempts to trace a linear cause-and-effect chain of events to a single identifiable etiology. In the traditional Chinese medicine framework, illness is understood as an overall pattern of a multiple of physical, psychological and environmental factors.

Two of the methods of defining and explaining natural phenomena by the ancient Chinese involve the concepts of Yin and Yang and 'the five phases'. The theoretical basis of traditional Chinese medicine stems from a system of metaphysics that focuses on the balance between two opposing forces: Yin and Yang. The concept of Yin and Yang is simple, but its meaning is profound. Yin and Yang are interdependent, existing in a constant state of dynamic balance. They can transform into each other, and are natural phenomena that also exist within the body. Yin is present in the qualities of cold, rest, passivity, dark, inward, decrease and female. Yang is associated with hot, activity, activity, light, outward, increase and male (Table 1). Health requires a balance of Yin and Yang within the body. Disease is

**Table 1** Yin and Yang are projected to all levels of the cosmos through a system of correspondences

| | *Yin* | *Yang* |
|---|---|---|
| Nature | Winter | Summer |
| | Dark | Bright |
| | Cold | Hot |
| | Night | Day |
| | Moon | Sun |
| | Rest | Activity |
| | Earth | Heaven |
| | Low | High |
| | Heaviness | Lightness |

| | | |
|---|---|---|
| Body | Female | Male |
| | Lower | Upper |
| | Interior | Exterior |
| | Front | Back |
| | Structure | Function |
| | Inhibition | Stimulation |
| | Deficiency | Excess |
| Medicine | Chronic disease | Acute disease |
| | Gradual onset | Rapid onset |
| | Cold | Heat |
| | Pale | Red |
| | Moist | Thirst |
| | Loose stool | Constipation |

characterized by a disharmony or a lack of balance between Yin and Yang.

The balance of Yin and Yang within the body promotes the flow of Qi (pronounced 'chee'). Qi is not easily translatable or defin-able, as a clear distinction between matter and energy is not made in Chinese metaphysics. It signifies power, movement, a tendency similar to energy. Qi is the functional, active part of the body. All living creatures result from the Qi of Heaven and the Qi of Earth. The union of the Qi of the Heaven and Earth creates the Qi of the human being. Qi is an energy that manifests concurrently on the physical and spiritual levels. Qi flows through a complex system of meridians throughout the body, maintaining life and health. These meridians are not defined by physical structures such as blood or lymphatic vessels, but by their function. The body is viewed as a dynamic system of organs connected by the flow of Qi within the meridians. Twelve different meridians are identified in traditional Chinese medicine, reflecting

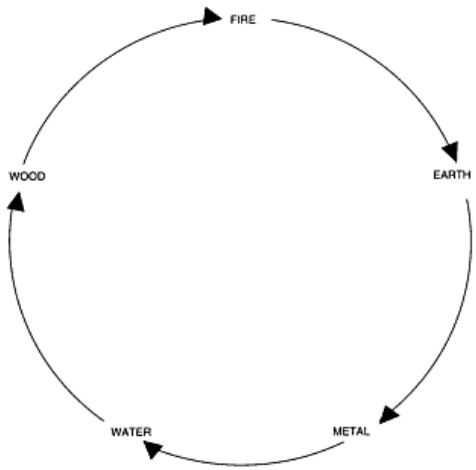


**Figure 1** The *sheng* cycle is a 'promoting/creating' cycle

either the body's anatomical or its energetic functions.

Illness results from inadequate flow of Qi through the meridians. The flow of Qi may be restored by the insertion of several very fine needles into a combination of points from the 365 classical acupuncture points that exist along the meridians. The manual twirling of these needles produces a sore, heavy, or numb sensation known as *De Qi* (obtaining Qi). Practitioners of traditional Chinese medicine observed that stimulating specific acupuncture points resulted in predictable responses in patients with a given pattern of signs and symptoms. The great treatises *Huang Di Nei Jin* (The Yellow Emperor's Internal Classic) guide the practitioner to select the correct points for a particular condition. Several treatments may be required over the course of weeks or months.

The theory of five phases is based on the notion that all phenomena in the universe are the products of the evolution of five substances: wood, fire, earth, metal and water. In traditional Chinese medicine, the theory of five phases corresponds with normal physiology, influences pathological changes and affects the management of ailments. An unidentified author once translated it as 'five elements'. The interactions between them are dynamic processes. 'Five phases' is a better translation, with all five phases interacting with each other.

The *sheng* cycle is a 'creating' cycle (Figure 1). Fire creates earth; earth creates metal; metal engenders water; water promotes wood; wood promotes fire. If there is an increase in wood, wood will then increase fire. If there is increase in fire, earth will increase metal. If there is an increase in earth, metal will then increase water. If there is an increase in metal, water will then increase wood. Each phase has a corresponding Yin and Yang channel, corresponding with meridians in the body. We can then strengthen each organ accordingly (Table 2).

The *ke* cycle is a controlling/restraining cycle. Wood splits earth; earth blocks water; water extinguishes fire; fire melts metal; metal cuts wood. The controlling sequence ensures that a balance is maintained among the five phases (Figure 2). The mutual generating and controlling relationship is a model of many self-regulating and balancing processes that exist in the human being and nature.

Practitioners of acupuncture routinely request the patient's detailed history and present illness in pursuing the diagnosis. In addition, attention is focused on the character of the pulse and the appearance of the tongue. In traditional Chinese medicine, there are six

**Table 2** Five phases (fire, earth, metal, water and wood) and their corresponding meridians

| *Fire* | *Earth* | *Metal* | *Water* | *Wood* |
|---|---|---|---|---|
| Heart/ pericardium | Spleen | Lung | Kidney | Liver |
| Small intestine/ *san jiao* | Stomach | Large intestine | Bladder | Gallbladder |

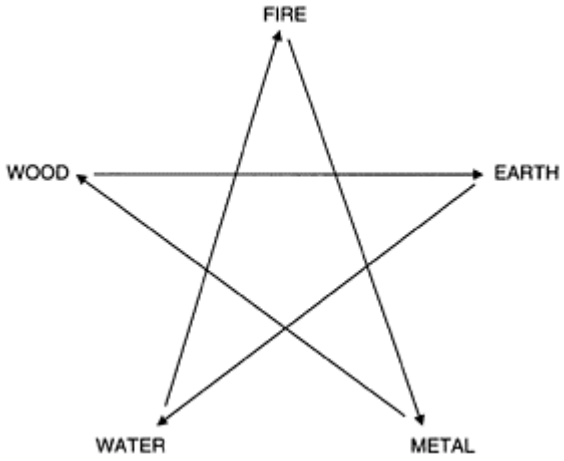


**Figure 2** The *ke* cycle of five phases

pathological factors that cause disease: wind, cold, heat, dampness, dryness and fire. The goal of the history and physical examination is to assess the patient's balance of Yin and Yang, and to gain insight into other symptoms. There are eight principal classifications of symptoms, which include Yin or Yang, superficial or deep, cold or hot, and deficient or excessive. The aim of therapy is to restore deficiencies or correct excesses in Qi, thus refurbishing health. Acupuncture, herbs and moxibustion are frequently used for preventive as well as therapeutic purposes.

Traditional Chinese medicine has evolved over the past three millennia and continues to be used today in China, throughout Asia and in communities around the world. The theory and practice of traditional Chinese medicine differs considerably from Western medicine, often making traditional Chinese medicine difficult to understand and accept. However, the lack of understanding of the specific biological mechanisms does not preclude its use and practice. The utility and validity of traditional Chinese medicine lie in the demonstration of its effectiveness. As with any therapy, however, properly conducted laboratory and clinical studies are necessary to establish the safety and effectiveness of traditional Chinese medicine.

The first European report on traditional Chinese medicine and acupuncture came from a 16th century Jesuit in Canton, China by Portuguese, Dutch, Danish and French missionaries. Earlier reports mentioned the techniques of diagnosis by feeling the pulses and looking at the tongue. Consuming herbs and tea or inserting needles were reported to promote health and prevent illnesses. Sir William Osler's *Principles and Practice of Medicine*, first published in 1892, recommended acupuncture for the treatment of sciatica and lumbago. In the 1901 edition of *Gray's Anatomy* the use of acupuncture for lumbago was noted. The interest in acupuncture in the USA started in the 1970s when James Reston described, in a front page article in *The New York Times*, how his postoperative pain from an emergency appendectomy had been alleviated by acupuncture. Since then, stories of the use of acupuncture for anesthesia during major surgery in China have been appearing in the Western press. This popular interest soon led to scientific efforts to test

the clinical effectiveness and elucidate the underlying physiological mechanism of acupuncture for analgesia. In the West, basic scientific and clinical research has focused on the use of acupuncture for the management of pain. Randomized controlled trials have not historically been part of traditional Chinese medicine and acupuncture, which was derived empirically through many years of experience.

## SCIENTIFIC EVIDENCE

Basic scientific research has focused on understanding acupuncture from a neurobiological perspective. One possible theory is that acupuncture inhibits the transmission of pain according to the gate-control theory put foreward by Melzack and Wall in 1965[2]. In this model, acupuncture may act by stimulating sensory A-β fibers, directly inhibiting the spinal transmission of pain by smaller A-δ and C fibers[3].

The subject of most basic research has been the relationship between acupuncture and the production of endogenous opioid peptides, such as endorphins and enkephalins, and stimulation of the endogenous descending inhibitory pathways. In human studies, analysis of cerebrospinal fluid (CSF) after acupuncture treatment showed elevated levels of serotonin, endorphins and enkephalins[4]. Although the mechanism of acupuncture analgesia is not entirely clear, a growing body of scientific knowledge indicates that 'the essence of acupuncture analgesia is mainly the activation of the endogenous antinociceptive system to modulate pain transmission and pain response'[5]. Low-frequency (2 Hz) and high-frequency (100Hz) electrical acupuncture selectively induces the release of enkephalins and dynorphins in both experimental animals and humans[6]. Peripheral stimulation of the skin or deeper structures activates various brain structures and/or the spinal cord via specific neural pathways[7]. An early human study by Mayer and colleagues indicated that acupuncture analgesia may be reversed by naloxone[8]. Similar findings were reported in animal studies. However, a subsequent human study by Chapman and co-workers failed to show evidence of naloxone reversal of analgesia[9].

Pomeranz and Stux offered a comprehensive theory which proposes that acupuncture activates small myelinated nerve fibers in the muscle, sending impulses to the spinal cord that activate centers in the spinal cord, midbrain and pituitary-hypothalamus to produce analgesia[10]. The spinal cord may use enkephalin and dynorphin to block incoming pain signals. In the midbrain, enkephalin may activate the raphe descending system, which inhibits pain transmission at the level of the spinal cord with the monoamines serotonin and epinephrine. The pituitary-hypothalamus may act to release β-endorphin into the blood and CSF to produce analgesia at a distance. The author postulated a similar mechanism, emphasizing the importance of the periaqueductal gray in initiating descending as well as ascending pain inhibitory pathways[5].

Functional magnetic resonance imaging (fMRI) has been utilized to investigate the effect of acupuncture in normal volunteers, to provide the foundation for the understanding of the mechanism of acupuncture. Correlations between the BL 67 *(Zhi Yin)* acupuncture

**Table 3** Size of acupuncture and electromyography needles in common use

| | *Gauge* | *Diameter (mm)* |
|---|---|---|
| Acupuncture needles | 42 | 0.14 |
| | 40 | 0.16 |
| | 38 | 0.18 |
| | 36 | 0.20 |
| | 34 | 0.22 |
| Electromyography needles | 30 | 0.30 |
| | 27 | 0.40 |
| | 26 | 0.45 |
| | 23 | 0.60 |

point with the visual cortex was investigated[11]. Acupuncture needle manipulation on the LI 4 *(Hegu)* point modulated the activity of the limbic system and subcortical structure revealed in fMRI[12]. There is individual variation in the cortical activation patterns elicited by electrical acupuncture stimulation. Real acupuncture elicited significantly higher activation than sham acupuncture over the hypothalamus and primary somatosensory-motor cortex and deactivation over the rostral segment of the anterior cingulated cortex. Minimum acupuncture elicits significantly higher activation over the medial occipital cortex[13].

## PRACTICAL GUIDE

A wide variety of acupuncture needles are available. In *Huang Di Nei Jing* (The Yellow Emperor's Internal Classic) *Ling Shu* described nine shapes of acupuncture needle. Most needles now used in clinical practice are made of stainless steel, although needles of other metals, such as gold, are also available. They may be disposable or reusable. Reusable needles must be sterilized by appropriate autoclave techniques between uses. Sterile disposable acupuncture needles are preferable in the current medical standard of practice. Needles vary from ½ inch to 5 inches (1–12cm) in length and from 36- to 42-gauge. A comparison of the size of electomyography (EMG) and acupuncture needles is listed in Table 3. A steel or plastic insertion tube might be used as a guide for the placement of the needle. The needle is

**Figure 3** Manual insertion of an acupuncture needle

tapped through the epidermis while the tube is in place. Deeper insertion is achieved by manipulation of the needle after the tube is removed (Figure 3).

Following insertion, stimulation of the acupuncture may be achieved manually or by use of electroacupuncture. Each acupuncture point has a prescribed depth of insertion. Manual techniques may involve the lifting and thrusting of the needle and/or twisting and twirling of the needle. Electroacupuncture achieves a similar effect by low-voltage electrodes attached to the needles. The intensity, pulse width and duration may be varied, in much the same way as in transcutaneous elec-trical nerve stimulation (TENS).

Relatively little pain results from the insertion of the needles. Most acupuncturists are skilled in the painless insertion of needles. In our experience, most children can accept acupuncture treatment well[14,15]. For various conditions, multiple acupuncture treatment sessions may be required over an extended period of time to demonstrate its effectiveness. Extended follow-up would be required to demonstrate statistical significance by studying large numbers of patients.

## RISKS OF ACUPUNCTURE

Acupuncture is extremely safe. Occasionally, a patient may have some bruising at an acupunc-ture site. The principal risk is infection from the use of improperly sterilized needles. Cases of hepatitis B[16], HIV infection[17] and fatality[18] have been reported. This can be avoided by using disposable sterile acupuncture needles and proper insertion of the needles.

A review of nine surveys showed that the most common adverse events were needle pain (1–45%), tiredness (2–41%), and bleeding (0.03–38%). Feelings of faintness and syncope were uncommon, with an incidence of 0–0.3%. Feelings of relaxation were reported by as many as 86% of patients. Pneumothorax was rare, occurring only twice in nearly a quarter of a million treatments[19]. A study of the adverse effects of 32000 acupuncture consultations in the UK revealed that the most common adverse events were bleeding, needling pain and aggravation of symptoms. None of these events was serious[20]. Another study involved a prospective postal audit of treatments undertaken,

1848 professional acupuncturists in the UK during a 4-week period in the year 2000. All were invited to record details of adverse events and mild transient reactions after treatment. Participating practitioners reported on 34407 treatments. There were no reports of serious adverse events. They reported 43 minor adverse events, a rate of 1.3 per 1000 treatments, which included severe nausea and fainting (12 cases), prolonged aggravation of the symptoms (seven cases), and pain and bruising (five cases). There were three avoidable events: two patients had needles left in, and one patient had moxibustion burns to the skin caused by practitioners' errors[21].

## CLINICAL USE OF ACUPUNCTURE

Systematic reviews from randomized controlled trials provide the best evidence for practicing medicine. This method is least subject to bias in assessing the efficacy of the therapy. Clinical research into acupuncture has largely consisted of uncontrolled trials for the treatment of chronic pain in adults. While beneficial results have been frequently demonstrated, the flawed design of many studies gives limited value to the results.

Several difficulties are inherent in the designing of valid blinded, randomized controlled trials of acupuncture[22,23]. The studies have to be, at best, single blind, as a trained acupuncturist must do the needling. Difficulties also arise in determining an appropriate placebo for the control group. Various studies have used 'sham' acupuncture (needles placed at incorrect or non-meridian sites), other devices (such as a non-functional TENS unit), or no treatment at all. This factor is important, since as many as 30% of subjects may respond positively to some placebos. There is little consistency in the literature pertaining to the criteria used for acupuncture research.

Sham acupuncture is commonly used for the control treatment in research trials involving acupuncture, but it presents a unique problem as a placebo. The well-outlined energy channels of the acupuncture meridian systems cover the entire body, linking Wei-Qi (defence Qi), Rong-Qi (growth and development Qi) and Yuan-Qi (the original Qi inherited at birth). As the meridian systems affect the entire body, the sham acupuncture does have some acupuncture effects. The placebo control implies the use of inert intervention. The sham acupuncture is different from a pure placebo. To try to address this difficulty, a placebo acupuncture needle has been developed. The placebo acupuncture needle retracts back into the handle of the acupuncture needle and does not penetrate the skin[24].

### Chronic pain

Richardson and Vincent[25] reviewed 27 controlled studies of acupuncture for treating acute and chronic pain, as well as several large uncontrolled studies. Of the patients, 50–80% showed that short-term data made assessment of long-term effectiveness difficult. In a metaanalysis of 14 randomized controlled trials of acupuncture for chronic pain in adults, Patel and colleagues found that, while few of the individual trials demonstrated statistically significant benefit from acupuncture, the pooled results for several subgroups attained statistical significance in favor of acupuncture[26].

### Low back pain

Low back pain is not well defined, but involves a non-specific category of complaints of various causes. In a meta-analysis of 12 randomized controlled trials, acupuncture was found to be superior to various control interventions for the management of low back pain[27]. A randomized controlled trial of acupuncture versus TENS for chronic low back pain in the elderly revealed that both were equally effective. Acupuncture may improve spinal flexion[28]. A randomized controlled study of 50 patients with low back pain showed that a significant decrease in intensity of pain occurred at 1 and 3 months in the acupuncture groups, compared with the placebo group. There was a significant improvement in return to work, quality of sleep and analgesic intake in subjects treated with acupuncture[29]. A recent randomized controlled study revealed significant improvement from traditional acupuncture in chronic low back pain as compared to routine care (physiotherapy), but not compared to sham acupuncture. The improvements included pain intensity, pain disability and psychological distress at the end of 12 weeks of treatment. At the 9-month follow-up, the superiority of acupuncture over the control condition had lessened[30].

### Headache

Acupuncture therapy for migraine headaches has also been reported to be effective in several adult studies[31,32]. A systematic review of 22 trials, including 15 migraine, six tension and one mixed, involving a total of 1042 patients, concluded that the existing evidence suggests that acupuncture has a role in the treatment of recurrent headaches[33]. In a randomized controlled trial of 168 women with migraine, acupuncture was shown to be adequate for migraine prophylaxis. Relative to flunarizine, acupuncture treatment exhibited greater effectiveness in the first months of therapy and superior tolerability[34]. Our experience also indicates that acupuncture can be a useful complementary therapy for the management of pediatric headache[35].

### Temporomandibular joint dysfunction

Three randomized controlled trials, involving 205 patients, of acupuncture treatment of temporomandibular joint dysfunction were all positive. Acupuncture may be an effective therapy for temporomandibular joint dysfunction. However, confirmation is still required, with more rigorous methods of trials[36].

### Neck pain

Several clinical reports have suggested that acupuncture might be useful for patients with neck pain. Fourteen randomized controlled trials involving 724 subjects with various causes of neck pain did not provide significant evidence in support of acupuncture for the treatment of neck pain[37]. There are too few trials of chronic neck pain of sufficient quality and homogeneity to be able to draw conclusions as to the effectiveness of the treatment. Several problems exist regarding the scoring system[38]. A randomized controlled study of 177 patients with chronic neck pain were randomly allocated to five treatments over 3 weeks with acupuncture ($n$=56), massage ($n$=60), or sham laser

acupuncture (*n*=61). The acupuncture patients received five treatments over 3 weeks. Acupuncture was shown to be an effective short-term treatment for patients with chronic neck pain.[39]

### Myofascial pain syndrome

Acupuncture may be useful for the treatment of chronic myofascial pain. In an uncontrolled study, Lewit reported immediate relief in 87% of cases and long-term benefit in at least 92 of 288 cases[40]. Melzack and colleagues reported a 71% correlation between acupuncture points and trigger points used in the treatment of myofascial pain[41].

### Carpal tunnel syndrome

Eleven patients with mild-to-moderate carpal tunnel syndrome were randomized into real and sham treatment series (each for 3–4 week). Real treatments used a red-beam laser (continuous wave, 15mW, 632.8 nm) on shallow acupuncture points on the affected hand, an infrared laser (pulsed, 9.4W, 904 nm) on deeper points on the upper extremity and cervical paraspinal areas, and microamps TENS on the affected wrist. The hand was treated behind a hanging black curtain without the patient knowing whether devices were on (real) or off (placebo). There were significant decreases in the McGill pain questionnaire (MPQ) score, median nerve sensory latency, and Phalen and Tinel signs after the real treatment series but not after the placebo treatment series. Real treatment trial patients were able to perform their previous work (computing, typing, handyman activities) and remained stable for 1–3 years[42].

### Neuropathic pain

Peripheral neuropathy is common in patients infected with human immunodeficiency virus (HIV). Neither acupuncture nor amitriptyline was more effective than placebo in relieving pain caused by HIV-related peripheral neuropathy[43].

### Stroke rehabilitation

Stroke is a main cause of disability and dependence in the elderly. Nine randomized controlled trials involved 538 patients with acute, subacute or chronic stroke. There is no compelling evidence to show that acupuncture is effective in stroke rehabilitation[44]. A multicenter, randomized, controlled trial involving 150 patients with moderate or severe functional impairment was performed in Sweden. At days 5 to 10 after acute stroke, patients were randomized to one of three intervention groups: acupuncture, including electroacupuncture; sensory stimulation with high-intensity, low-frequency transcutaneous electrical nerve stimulation that induces muscle contractions; and low-intensity (subliminal) high-frequency electrostimulation (control group). A total of 20 treatment sessions were performed over a 10-week period. At 3-month and 1-year follow-ups, no clinically important or statistically significant differences were observed between groups for any of the outcome variables. Treatment during the subacute phase of stroke with acupuncture or TENS with muscle contractions had no beneficial effects on

functional outcome or life satisfaction[45]. A meta-analysis of 14 trials, involving 1213 patients, suggested that acupuncture had no additional effects on motor recovery but had a small positive effect on disability[46].

### Spinal cord injury

The use of concomitant auricular and electrical acupuncture therapies, when implemented early in acute spinal cord injury, can contribute to significant neurological and functional recoveries. A randomized controlled study of 100 patients with traumatic spinal cord injury revealed significant improvements in neurological and functional scores in the acupuncture group compared with scores at the initial admission period, when assessed during the time of hospital discharge and at the 1-year post-injury followup. A greater percentage of patients in the acupuncture group also recovered to a higher ASIA impairment grading[47].

### Seizure

Twenty-nine patients with chronic intractable epilepsy completed the study[48]. They were randomized into two groups; 15 were given classical acupuncture and 14 were given sham acupuncture. There was a reduction in seizure frequency in both groups, which did not reach a level of statistical significance. There was also an increase in the number of seizure-free weeks in both groups[48].

### Parkinson's disease

A study of 201 patients with Parkinson's disease revealed that acupuncture was one of their most commonly used forms of complementary and alternative medicine[49]. A study of 20 patients with Parkinson's disease revealed that acupuncture was safe and well tolerated. A range of Parkinson's disease and behavioral scales failed to show improvement following acupuncture other than sleep benefit, although patients reported other symptomatic improvements. Acupuncture treatment resulted in improvement in sleep and rest[50].

### Complex regional pain syndrome

Reports have appeared about the benefits of traditional acupuncture therapy and auricular therapy in treating complex regional pain syndrome (CRPS), formerly known as reflex sympathetic dystrophy[51,52]. However, each of these reports involved only one to five patients in uncontrolled studies. In addition, the intermittent natural history of pain in CRPS makes reassessment of the treatment effect difficult.

### Depression

Patients suffering from major depression were treated with electroacupuncture for 4 weeks. Neuropeptide Y concentration in plasma decreased during the first 2 weeks of treatment. The results correspond to an assumed antidepressive effect of

electroacupuncture[53]. Women with major depression were randomly assigned to one of three treatment groups. Specific treatment involved acupuncture treatments for symptoms of depression; non-specific treatment involved acupuncture for symptoms that were not clearly part of depression; and a wait-list condition involved waiting without treatment for 8 weeks. A comparison of the acute effect of the three 8-week treatment types showed that patients receiving specific acupuncture treatments improved significantly over those receiving the sham acupuncture treatments, and marginally more than those in the wait-list condition. Acupuncture was shown to provide significant symptom relief in depression, at rates comparable to those of psychotherapy or pharmacotherapy[54]. Another study involved 70 inpatients with a major depressive episode randomized into three different treatment groups: true acupuncture, sham acupuncture and a control group. All three groups were pharmacologically treated with the antidepressant mianserin. Patients who experienced acupuncture improved slightly more than patients treated with mianserin alone. Additionally, applied acupuncture improved the course of depression more than pharmacological treatment with mianserin alone[55].

### Nausea and vomiting

Acupuncture is commonly used for the management of nausea and vomiting. Stimulation of the PC-6 points (*Nei Guan* acupuncture point; the Chinese means 'Gate of the Internal Organ') by acupuncture needles, electrical apparatus, pressure, or magnets is used to treat nausea and vomiting due to sea-sickness, pregnancy, or from the side-effects of surgery or chemotherapy. The PC-6 point is located 2 inches (5 cm) above the transverse crease of the wrist, between the tendons of the long palmar muscle and the radial flexor muscle of the wrist. A systematic review was conducted of 33 randomized controlled trials of acupuncture and acupressure. The results of 27 of the trials were positive[56]. In a laboratory study of experimentally induced motion sickness, 64 volunteers were placed in an 'optikokinetic drum' (the drum's inner surface was covered with alternating black and white stripes to increase visual-induced motion sickness). The PC-6 acupressure group showed significantly reduced intensity in subjective and objective symptoms of visual-induced sickness[57].

### Sleep disturbance

One randomized controlled trial of 40 patients with primary sleep disturbance reported that acupuncture was better than sham acupuncture for objective and subjective sleep disturbance[58]. Several uncontrolled reports suggest that acupuncture can promote sleep, but rigorous evidence is limited.

### Acute pain

Acupuncture may be more useful in predictable situations involving acute pain, such as dental procedures and postoperative pain, or in the setting of medical conditions with recurrent episodes of acute pain, such as sickle-cell crisis and recurrent abdominal pain. Although effective treatment is available in many cases (e.g. local anesthetics for dental procedures, opioids for severe postoperative pain), sideeffects, such as respiratory

depression, may be seen. Taub and colleagues used acupuncture for the treatment of dental pain in a singleblind, randomized controlled trial in 39 adult patients undergoing dental restoration for cavities[59]. Patients were randomized between real and sham acupuncture. Seventy per cent of the experimental group reported good or excellent pain reduction, and 53% of the control group reported good or excellent pain reduction. The results for the two groups showed no statistically significant difference. Systematic review has shown that acupuncture is effective in relieving dental pain[60]. A study of the effect of acupuncture in pain after lower abdominal surgery revealed that preoperative treatment with low- or high-frequency electro-acupuncture could reduce the postoperative analgesic requirement and decreased the sideeffects of systemic opiates[61].

## REFERRING PATIENTS FOR ACUPUNCTURE TREATMENT

It is important to distinguish the difference between disease and illness. The disease is what the physician can diagnose; the illness is what the patient feels. There is no cure for numerous neurological diseases; however, acupuncture can be used to treat various illnesses associated with neurological disorders or to conquer the side-effects associated with conventional medical therapies. Further larger scale randomized controlled trials are still needed to evaluate the efficacy of the therapy.

Licensing guidelines for the practice of acupuncture are determined individually by each state of the USA. The National Commission for the Certification of Acupuncturists (NCCA) has developed standards for training and certification. Most states use the NCCA examination process to license acupuncturists. Some states require licensed physicians' supervision of acupuncturists. This includes confirming the diagnosis of the patient prior to treatment. Other states allow licensed acupuncturists to practice independently. It is estimated that there are approximately 14000 licensed acupuncturists in the USA. Most acupuncturists receive 2–3 years of academic training, including supervised clinical experience in the treatment of a variety of medical disorders.

Over the past several years, the use of traditional Chinese medicine has become more common and accepted in the USA. Some of the Health Maintenance Organization (HMO) insurance plans have begun to cover acupuncture treatments for their patients. Some workmen's compensation boards and personal injury insurance policies will also cover acupuncture. If there is a rise in the number of insurers willing to reimburse for acupuncture therapies, patient utilization is likely to continue to increase in the future[62].

Most states allow physicians to practice acupuncture after they have received appropriate training. A minimum of 300 h of formal training is considered necessary. The American Academy of Medical Acupuncture is one of the largest physician acupuncturist associations. The American Board of Medical Acupuncture has developed a comprehensive board certification process for physician acupuncturists. It is estimated that there are 3000 trained physician acupuncturists in the USA today.

How can we best advise patients with neurological disorders who are interested in acupuncture? The practitioner should discuss with the patients their treatment preferences and outcome expectations. It is important to thoroughly review with the patients the process of acupuncture, including its safety and efficacy. Patients should be referred to

qualified acupuncture providers, and follow-up appointments scheduled to monitor their treatment response.

## ACKNOWLEDGEMENT

The author would like to thank Ms. Margaret Munro Lyons for her assistance in the preparation of this manuscript.

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# 7
# Naturopathic medicine in neurological disorders

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*Complementary Therapies in Neurology: An Evidence-Based Approach*
Edited by Barry S.Oken
ISBN 1-84214-200-3 

## NATUROPATHIC MEDICINE

John Sheel and Benedict Lust founded and named the practice of naturopathy at the end of the 19th century. Their aim was to coalesce several traditions of natural medicine including herbalism, diet therapy, hydrotherapy and homeopathy into a single practice that contrasted with the often harmful chemical interventions of the time. Naturopathic medicine is now a worldwide profession in the USA, Germany, Canada, the UK, Australia and India. In the USA and Canada, naturopathic medicine is a primary health-care profession which functions to promote health, and to prevent, diagnose and treat disease. The intent of a naturopathic doctor (ND) is to stimulate the self-healing capacities of the individual by using a number of therapeutic modalities which include botanical medicines, clinical nutrition and nutritional supplements, homeopathy, physical medicine (physiotherapy, hydrotherapy, manipulation) and psychological counseling. Treatment is individualized for the particular patient's condition and capacities rather than for just a disease entity. Typically a combination of treatments is applied and continuously adjusted over time as the patient's condition changes. The practice is guided by principles most recently articulated by the American Association of Naturopathic Physicians (AANP) in 1989:

(1) *First, do no harm.* Utilize methods and substances that minimize harm. Apply the least force for diagnosis and treatment.
(2) *Nature heals (Vis medicatrix naturae).* Organisms are inherently self-organizing. It is the physician's role to support this process by removing obstacles to health and contributing to the creation of a healthy internal and external environment.
(3) *Identify and treat the cause.* Symptoms may represent the body's attempt to defend itself and to adapt and recover. The physician's optimal approach is to seek and treat the causes of disease rather than suppress the symptoms.
(4) *The doctor is a teacher.* The physician's role is to educate the patient and emphasize self-responsibility.

(5) *Treat the whole person.* The multifactorial nature of health and disease requires attention to the physical, mental, emotional, spiritual, social and ecological aspects of our nature. Diagnosis and treatment that are constitutional and holistic are among the foundations of naturopathy.
(6) *Prevention.* The prevention of disease by the attainment of optimal health is a primary objective.

Naturopathic medicine is practiced as either a complement or an alternative to conventional medicine under different circumstances. Licensed NDs are considered by many to be the most broadly trained in complementary and alternative medicine (CAM) practices and by some to be the best prepared for integration into the mainstream health-care system, owing to their education in both conventional biomedical sciences and a broad range of natural medicine modalities.

### Education and training

Licensed NDs in the USA and Canada have almost always graduated from one of five accredited 4-year naturopathic colleges (Table 1). The four US colleges have been accredited by the Council for Naturopathic Medical Education (CNME) which provides for a standardized educational process. The 4-year training provided at these post-baccalaureate colleges includes lectures and laboratory work in the biomedical sciences and natural therapeutics. The first 2 years cover biomedical sciences and diagnostics including anatomy, biochemistry, physiology, histology, neuroscience, pathology, pharmacology, laboratory and clinical diagnosis and naturopathic philosophy. There are overviews as well on the philosophy and approach of other holistic medical systems such as ayurvedic medicine, and traditional Chinese medicine (TCM). The remaining 2 years focus on naturopathic therapeutic modalities with an emphasis on clinical coursework and experience. Courses include

**Table 1** Accredited naturopathic colleges in the USA and Canada

| *Name* | *Address and website* |
|---|---|
| Bastyr University | 14500 Juanita Drive, NE,<br>Kenmore, WA 98028<br>(425) 823–1300<br>http://www.bastyr.edu/ |
| National College of Naturopathic Medicine (NCNM) | 049 SW Porter Street,<br>Portland, OR 97201<br>(503) 499–4343<br>http://www.ncnm.edu/ |
| South West College of Naturopathic Medicine (SCNM) | 2140 East Broadway,<br>Tempe, AZ 85282<br>(480) 858–9100<br>http://www.scnm.edu/ |
| University of Bridgeport, College of Naturopathic Medicine | 60 Lafayette Street, |

| | |
|---|---|
| | Bridgeport, CT 06601<br>(203)5764109<br>www.bridgeport.edu/naturopathy |
| Canadian College of Naturopathic Medicine | 1255 Sheppard Avenue, E,<br>North York, ON M2K 1E2<br>(416)498–1255<br>http://www.ccnm.edu/ |

botanical medicine, homeopathy, physical medicine, diet, nutritional supplementation, psychological counseling, minor surgery, obstetrics and gynecology, neurology, urology, dermatology, oncology, endocrinology, rheumatology, pediatrics and geriatrics. The five naturopathic colleges also house clinics for naturopathic treatment for a wide variety of disease conditions. Practical clinical training occurs primarily in these clinics where licensed NDs supervise and mentor students during clinical rotations. Naturopaths may elect to undergo additional training in midwifery or TCM. These modalities often require separate licensing and certification processes. All the naturopathic colleges have postgraduate residency programs, but currently post-graduate residency is not required as part of training and licensing. Often, graduates will join the practices of experienced clinicians before setting out on their own.

## Licensing and scope of practice

In the USA a naturopathic physician must be licensed to practice in at least one of 11 states and two US territories (Table 2). In Kansas and the District of Columbia, NDs must register in order to practice. In Canada, naturopathic physicians are licensed to practice in four provinces. The license is typically broad, allowing naturopathic doctors (NDs, or in some jurisdictions NMDs) to diagnose and treat disease using any natural means. In Arizona and British Columbia, acupuncture is a part of the regulated practice; elsewhere, NDs must obtain an additional license to practice acupuncture. Prescriptive drugs of natural origin, minor surgery and midwifery are permitted in many jurisdictions, and most licensed states require annual proof of continuing medical education (CME) to maintain licensure (Table 2). The requirements necessary for obtaining a license to practice include graduation from an accredited naturopathic college, passing standardized licensing examinations (Naturopathic Physicians Licensing Examination) (NPLEX), and state filings and licensing fees[1].

NPLEX is the standard examination used by all licensed US states and Canadian provinces. The two-part examinations include basic and clinical sciences. The first is taken after a candidate has passed basic science courses, usually after the second year of naturopathic school and includes anatomy, physiology, pathology, biochemisty, microbiology and immunology. The clinical examination is taken after graduation from an accredited naturopathic college and covers clinical training and knowledge in the various therapeutic modalities. The clinical examinations include clinical and physical diagnosis, laboratory diagnosis and diagnostic imaging, botanical medicine, pharmacology, nutrition, physical medicine, homeopathy, minor surgery, psychology and lifestyle counseling, and emergency medicine. Individual states may give additional examinations on acupuncture, minor surgery and jurisprudence.

There are approximately 2000 licensed NDs in the USA who have been trained in accredited in-residence 4-year post-baccalaureate institutions[2]. There may be several thousand additional unlicensed naturopaths whose training is highly variable (e.g. correspondence schools, self-taught)[1]. The two groups have different professional associations. Insurance coverage is often available for services of NDs in licensed states but rarely for the unlicensed. In general, licensed NDs seek to extend regulation of the profession to all states and unlicensed practitioners tend to resist regulation.

The scope of naturopathic practice is stipulated by state law and therefore varies from state to state. In general, naturopaths are licensed as primary health-care providers and are allowed to diagnose and treat most acute and chronic conditions that can be treated in an out-patient setting. Naturopaths are licensed to practice natural therapies which include substances of natural origin; some states allow substances which are bioidentical to naturally occurring molecules. The modalities typically included are those which form the core of naturopathic therapeutics: botanical medicine, clinical nutrition, nutritional supplements and substances occurring in the body (e.g. hormones), homeopathy, physical medicine (physiotherapy,

**Table 2** US States and Canadian provinces licensing naturopathic physicians

| | *Primary care providers* | *Prescription drug use* | *Minor surgery* | *Midwifery* | *Venipuncture* | *X-ray* | *CME* |
|---|---|---|---|---|---|---|---|
| Licensed states in the USA | | | | | | | |
| Alaska | X | | | | X | X | |
| Arizona | X | X | X | X | X | X | X |
| Connecticut | X | | X | X | X | X | |
| Hawaii | X | X | | X | X | X | |
| Kansas | X | | | | X | X | |
| Maine | X | X* | X | | X | X‡ | X |
| Montana | X | X | | x† | X | X‡ | X |
| New Hampshire | X | X* | | x† | X | X | X |
| Oregon | X | X | X | X† | X | X | X |
| Utah | X | X | X | X | X | X | X |
| Vermont | X | X* | | X | X | X | X |
| Washington | X | X | | X† | X | X | X |
| Puerto Rico | X | | | | | X‡ | X |
| Virgin Islands | X | | | | | | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| District of Columbia | X | | | | | | |
| Licensed Canadian provinces | | | | | | | |
| British Columbia | X | | X | | | | |
| Manitoba | X | | | | | | |
| Ontario | X | | | | | | |
| Saskatchewan | X | | | | | | |

CME, continuing medical education; [*]limited; [†]with extra training and certification; [‡]order but not perform

hydrotherapy, manipulation) and psychological counseling. Therapeutic scope may include prescriptive use, minor surgery and diagnostic radiographics (performing X-rays and ordering X-rays, magnetic resonance imaging (MRI), computerized tomography (CT) scans), but again these interventions would be stipulated per state by law (Table 2).

## Clinical approach

A naturopath will focus on attaining optimal health for an individual rather than only on a disease entity. Optimal health will vary from person to person, therefore a naturopath will work with their patients to define what optimal health is for them, to identify areas needing help and to put together a therapeutic plan to improve functionality, reduce risks and reach health goals. Care for most individuals will include diet (the assurance of adequate but not excessive macro- and micronutrients, fiber and water), exercise and stress management as a base. Optimization in chronic neurological diseases will rarely mean curative therapeutics but will encompass slowing progression, symptomatic and rehabilitative care, increasing functionality, decreasing risks of concomitant diseases and enhancing coping skills. The therapeutic regimen will often include the healthsupportive use of nutritional supplementation, homeopathy, botanicals and physical medicine. Regimens are almost always combinations of treatments individualized for a patient. In general, naturopaths tend to view a healthy body as one that reflects a set of well-functioning health-sustaining capacities. Improving the function of the body's health systems may be sought in at least the following functions[3] which may relate directly or indirectly to neurologic disease.

### *Gastrointestinal function and integrity*

Maldigestion and suboptimal nutrition contribute to cellular imbalances that can result in acute and chronic disease conditions. Digestive enzymes and herbs can help improve maldigestive problems and improve absorption of nutrients from foods. A healthy diet regimen will optimize the amount and type of nutrients obtained through foods.

### *Detoxification*

A consequence of modern industrial society is the exposure to a variety of toxic substances (e.g. pesticides, heavy metals, endocrine disruptors). Many of these substances can be stored in fat, tissues and bone and are associated with health problems including neurological disorders (e.g. pesticide exposure and increased risk of parkinsonism[4–6]). Endogenous toxins may also present as a burden. Naturopaths will seek to reduce exposure, decrease the burden and strengthen eliminative organs. Therapies that help to decrease the burden of toxic chemicals in the body include hydrotherapy, exercise, fluids, herbs and nutritional supplements that support liver detoxification pathways and chelation.

### *Cellular regeneration and repair systems*

Adequate sleep, decreasing stress and nutritional supplementation can improve the body's ability to repair and regenerate cells and tissues. Stress can include musculoskeletal imbalances which may cause not only chronic pain directly, but neural, vascular and muscular dysfunction which can aggravate symptoms and prevent healing in the central and peripheral nervous systems.

### *Endocrine and regulatory systems*

Special foods, nutrients, herbs, hormone precursors and lifestyle changes are used to alter endocrine balance.

### *Strengthening and balancing the immune system*

Optimal immune function can be attained by identifying and eliminating factors that can damage the immune system (e.g. chronic stress, pathogens, nutritional factors). Hyperinflammatory states are seen in chronic conditions such as allergies, eczema and multiple sclerosis and increasingly appear to be implicated in Alzheimer's disease. Key to bringing balance to the immune system is through diet with supportive help from nutritional supplements and herbs, especially antioxidants and fatty acids.

### *Emotional and spiritual factors*

A person's beliefs and aspirations, family life and spiritual values have a profound impact on health. Emotional stress emanating from an imbalance in any of these areas can negatively impact health. Practices such as prayer and meditation can decrease stress and have positive emotional and physiological benefits.

Although this is a simplification of important naturopathic strategies and none of these approaches is a panacea, weakness in any of the systems will result in the susceptibility to disease which can accelerate decline or retard recovery. In addition to a conventional review of systems, a naturopath will review a person's lifestyle habits and patterns of symptoms to identify any weakness(s) that can be treated. Such examination takes time. A survey designed to explore the practice characteristics of a variety of CAM practitioners reported that the mean number of hours per week of direct patient contact

for naturopaths and acupuncturists was 25 h, while both types of practitioners had a mean number of 30 patients per week[7]. A typical office visit with a naturopath will last 30–60 min per patient. Treatment regimens are rarely static and will often be adjusted over time and, as indicated, combine modalities. Such regimens take time for both the practitioner and the patient, as they learn what therapies work and how to effect the behavioral changes and develop the adherence required.

## NATUROPATHIC MODALITIES

A brief overview follows of the main modalities practiced by NDs which include, as mentioned above, botanical medicine, diet (nutritional counseling), nutritional supplements, homeopathy, physical medicine (physiotherapy, hydrotherapy, electrotherapy, manipulation) and psychological counseling. There is a brief review of human trials that have been conducted for some neurological conditions for that modality. However, since many of the modalities of naturopathy are more completely described in other chapters in this book, we will only review the clinical evidence for efficacy in diet, some nutritional supplements (excluding vitamins and essential minerals) and homeopathy. Because it is not addressed substantively in other chapters of this book, a brief introduction to homeopathy is also included.

### Botanical medicine

Naturopaths are primarily trained in the European and North American botanical medicine traditions augmented by exposure to the indigenous botanical approaches of Asia, Africa, and Central and South America. They are the bearers of the eclectic tradition of herbal medicine, a medical movement of the late 19th and early 20th centuries, that was the most modern and detailed expression of herbal medicine in the USA but which had almost died out by the 1930s. The basic naturopathic training in botanicals includes historical use, disease indications, mechanism of action (if known), active constituents (if known), adverse reactions and contraindications, and drug interactions (if known) of about 200 botanicals. As botanicals come in many formulations (e.g. herbal extracts by various solvents, dry whole herb, standardized extracts, etc.) dosing may differ for different preparations. This is important, as many naturopaths continue to produce their own formulations of herbal tinctures. They may use a single herb or a combination of herbs to treat a particular disease condition. Combination herbal formulas are much more frequently used. Combinations of two to five herbs are often used in a formula for either acute or chronic conditions.

An interesting class of herbs that are frequently used for neurological conditions are the ‘nervines’. Nervines might be tonic, relaxant, or stimulant[8]. Skullcap *(Scutellaria lateriflor),* with the (somewhat dated) indications of ‘epilepsy, hysteria, nervous exhaustion, chorea, delirium tremens, tremors, spasms, twitching of muscles, hyperesthesia, neuralgia, convulsions’[9], would be among the relaxants, as would *Valerian* and *Passiflora incarnata.* Siberian ginseng *(Eleuthrococcus sinensis)* and gotu kola *(Centella asiastica)* might be considered stimulant nervines. However, besides immediate effects on symptoms, the most important part of a nervine’s action is neurotropic and

nutritive (tonic) by altering the internal environment to support the physical structure and functional integrity of neurons, and central and peripheral glial cells and their electrochemical signaling systems. The adaptogens, mostly from Asian traditions (the ginsengs, *Withania somnifera)*, are also considered tonic nervines. This tonic function of herbs is common across herbal traditions and is a class of mechanisms perhaps inadequately attended to among pharmaceutical approaches to neurological disorders.

## Diet (clinical nutrition)

Naturopaths attend to dietary assessment including macro- and micro-nutrient content in foods, individual responses to diets and specific foods and in the application of a variety of therapeutic diets. The use of diet to improve health is a therapeutic foundation in naturopathic medicine as it encompasses aspects of all six of the naturopathic principles. The types of diet that NDs use are highly variable and may include, on a case-by-case basis, low fat, elimination and challenge (hypoallergenic), glutenfree, dairy-free, blood type diet, vegetarian and fasting (juice, water).

Clinical evidence evaluating the influence of diet in neurological disease includes the following examples.

### *Epilepsy: the ketogenic diet*

The ketogenic diet is a high-fat, low-carbohydrate diet that was developed decades ago but which has recently come under consideration in intractable cases. Typically the ratio is 4 g fat to 1g of protein and carbohydrates combined. There have been many studies reporting a sig- nificant decrease in seizures of children with severe epilepsy that were treated with the ketogenic diet[10–12]. Although the diet is highly successful in decreasing seizures in difficult-to-treat epileptic children, compliance with the diet is often an issue[13]. There is evidence that it may increase the frequency of kidney stone formation in those on the diet[14].

### *Migraine headaches: hypoallergenic diets (elimination/challenge diet)*

The rationale for use of this type of diet for migraine headaches is that food allergies cause platelet degranulation and histamine release that can precipitate vasomotor instability and subsequent migraine[15]. There are a number of studies that have reported a benefit in subjects who suffer from migraines and have eliminated foods that might elicit a migraine[16–20]. The elimination diet requires that a person go on various versions of an oligoallergenic restricted diet (a typical diet may be primarily lamb and rice for a period of 7–10 days) after which they systematically re-introduce food groups to identify foods that will elicit a migraine. Once a food that triggers a migraine is identified, the food is taken out of the diet for a period of time and is re-introduced in smaller quantities. The strategy is not to stay on a highly restricted diet but to identify allergenic foods and to decrease the amounts and frequency of these foods consumed.

*Multiple sclerosis: the Swank diet*

There have been a number of epidemiological studies assessing associations between dietary factors and the risk of developing multiple sclerosis (MS). A number of epidemiological studies have reported a significant positive association between risk of MS and consumption of animal fat[21,22]. Dr Roy Swank has provided evidence that a diet low in saturated fats (less than 15 g/day) combined with cod liver oil supplementation, maintained over a long period of time, tends to retard the disease process, reduce the number of attacks and decrease mortality[23,24]. Oneopen-label pilot clinical trial evaluated the effects of a diet low in saturated fats supplemented with fish oil, vitamin B-complex and vitamin C in subjects with newly diagnosed relapsing-remitting MS[25]. After 2 years of this regimen the study reported a significant decrease from baseline values of relapse rates and disability scores. Preliminary reports from a recent randomized placebo-controlled pilot study evaluating a diet very low in saturated fat (less than 15%) supplemented with fish oil capsules found that, when compared with subjects following the American Heart Diet (less than 30% saturated fat) supplemented with placebo oil capsules, the treatment group had a significant decrease in relapse rate, disability and a decrease in two inflammatory cytokines[26]. These studies suggest that a diet very low in fat combined with fish oil supplementation may help to decrease relapse rates and increase time to disability in people with MS.

## Nutritional/dietary supplementation

Many naturopaths use a variety of nutritional supplements usually as an adjunct to fundamental lifestyle therapies, such as diet, exercise and stress reduction (counseling) to address a specific symptom or condition. The Food and Drug Administration (FDA) under the Dietary Supplement Health and Education Action (DSHEA) of 1994 defines a dietary substance as ‘a product (other than tobacco) that is intended to supplement the diet that bears or contains one or more of the following dietary ingredients: a vitamin, a mineral, an herb or other botanical, an amino acid, a dietary substance for use by man to supplement the diet by increasing the total daily intake, or a concentrate, metabolite, constituent, extract, or combinations of these ingredients’ (FDA website, http://vm.cfsan.fda.gov/~dms/dietsupp.html). Under the DSHEA, dietary supplements are considered foods and not drugs and therefore regulated by the FDA as foods. Examples of substances that are considered dietary supplements include: fish, flax, evening primrose and borage oils, glandulars (usually made from animal sources), enzymes, melatonin and dehydroepiandrosterone (DHEA) (although these are hormones they are regulated and sold as dietary supplements in the USA), garlic capsules, soluble fiber, coenzyme Q10 (CoQ-10), L-carnitine, 5-hydroxytryptophan (5-HTP), etc. Obviously this is just a small fraction of the number and types of existing dietary supplements; the associated effects indicated below are rarely definitive.

### *Alzheimer's disease/dementia: omega-3 fatty acids*

Docosahexaenoic acid (DHA, a component of omega-3 fatty acids, is the major polyunsaturated fatty acid (PUFA) present in the phospholipid fractions of the brain and appears to exert a positive role in both membrane fluidity and long-term potentiation (a process necessary for memory)[27,28]. Cold-water fish and fish oil contain a high proportion of the omega-3 fatty acids and therefore contain a higher relative proportion of DHA and eicosapentaenoic acid. There is evidence from one epidemiological study that an increase in fish consumption is associated with a decrease in risk for Alzheimer's disease (AD)[29]. Several studies have reported a decrease in peripheral and central nervous system (CNS) fatty acid levels in patients with Alzheimer's disease, compared to controls. These studies measured DHA and PUFA levels in postmortem brains, cerebral spinal fluid (CSF) and in plasma of patients with Alzheimer's disease[30–32]. All these studies suggest a relationship between a decrease in PUFA levels, specifically DHA, and Alzheimer's disease pathology.

There have been at least two clinical trials evaluating the effectiveness of essential fatty acids (EFA) and DHA supplementation for dementia. The first was a double-blind, placebo-controlled trial of patients diagnosed with Alzheimer's disease ($n$=100)[33]. The treatment group was given a mix of omega-6/ omega-3 fatty acids at a 4:1 ratio in which they received about 0.5 g/day of this fatty acid mixture for 4 weeks. There were no cognitive measures in this study, and subjects were rated on 12 behavioral variables by their guardian. The results of this study showed that a short treatment with EFA improved mood, cooperation, appetite, sleep, ability to navigate in the home, and short-term memory as reported by the subject's guardian. Although this study showed a positive benefit from short term EFA supplementation there were no objective measures in this study and no standard testing of cognitive function (e.g. Alzheimer's Disease Assessment Scale-cognitive subtest, Mini-mental State Examination (MMSE). The second, a double-blind placebo-controlled pilot study, evaluated the effects of 1 year of supplementation of 0.72 g of DHA/day on elderly subjects suffering from moderately severe dementia as a result of thrombotic cerebrovascular disease[34]. Mean MMSE scores were comparable between the two groups at baseline (control=19.7, DHA=20.1). A significant increase in MMSE score was reported after 6 months of supplementation (control=19.6, DHA=22.2, $p$<0.05). There was a significant increase in both serum DHA and eicosapentaenoic acid levels after 3 months of supplementation. Omega-3 fatty acids have shown effects in bipolar disorder, epilepsy, Huntington's disease, and MS, suggesting broad neurological effects not yet fully elucidated.

### *Amyotrophic lateral sclerosis: creatine*

Seven days of supplementation with creatine 20 g resulted in a transient increase in maximal voluntary isometric muscular contraction and fatigue in 28 patients[35].

### *Bipolar disorder*

Four months of treatment with 9.6 g/day of omega-3 fatty acids or olive oil in a blinded, randomized study demonstrated a significantly longer period of remission in 30 bipolar patients and improvement in almost all measures.

### *Depression: ethyl-eicosapentaenoic acid*

There are two double-blind placebo-controlled pilot studies that have reported a significant improvement in depression in people on stable doses of antidepressants after 1–3 months of ethyl-eicosapentaenoic acid (E-EPA) supplementation[36,37]. The effective dose ranged from 1 to 4 g of E-EPA per day.

### *Depression: L-acetylcarnitine*

Two small studies in elderly depressed patients ($n$=24 and 28) showed effectiveness without adverse effects[38,39].

### *Depression: dehydroepiandrosterone*

There are two small controlled pilot studies of DHEA in depressed adults that have reported benefit for that hormone[40,41].

### *Epilepsy: melatonin*

A small body of evidence suggests that melatonin may be useful in epilepsy[42–44]. Melatonin has effects in sleep disorders and perhaps in chronic headache and may prove of use in depression and irritability, suggesting broad CNS effects.

### *Epilepsy: polyunsaturated fatty acids (especially omega-3 fatty acids)*

In five patients, a reduction in frequency and intensity of epileptic seizures resulted from adding 5 g of a 65% omega-3 fatty acid spread at breakfast for 6 months[45]. Omega-3 fatty acids are increased in epileptic children on the ketogenic diet and correlate with resultant decreased seizure activity[46]. Animal studies also show modulation of seizure activity with PUFA[47–49].

### *Headache: 5-hydroxytrytophan*

5-HTP, a serotonin precursor, showed moderate efficacy and remarkable safety compared to placebo in 31 patients with chronic primary headache[50] and in 78 patients with chronic tension headaches[51]. In preference to methysergide or propranolol, owing to their side-effects, 5-HTP may be useful in reducing the frequency or intensity of migraines for some patients[52,53].

### *Huntington's disease: ethyl-eicosapentaenoic acid*

The ethyl-ester of eicosapentaenoic acid showed significant ($p$<0.03) benefit in the orofacial component of the United Huntington's Disease Rating Scale in a very small controlled study of seven patients[54]. However, all patients on treatment improved, while all patients on placebo deteriorated.

### *Insomnia: melatonin*

Although melatonin is a hormone, it is sold and regulated as a dietary supplement in the USA. There are a fair number of studies demonstrating its effectiveness for insomnia[55–65], primarily in improving sleep latency. Its ability to prevent jet-lag and concomitant sleep disruption is well-established[66].

### *Multiple sclerosis: omega-3 fatty acids*

There have been two studies evaluating the effects of omega-3 fatty acid supplementation in MS. One was an open-label trial evaluating the effects of fish oil (3 g/day) on inflammatory cytokine levels in 20 subjects with MS and 15 age-matched healthy subjects[67]. After 3 and 6 months of fish oil supplementation there was a significant decrease in the levels of soluble IL-1β ($p$<0.03), TNF-α ($p$<0.02), IL-2 ($p$< 0.002) and IFN-γ ($p$<0.01) in the unstimulated peripheral blood mononuclear cells (PBMC) of both groups. A significant decrease was observed after 3 and 6 months of supplementation in the levels of soluble IL-1β ($p$<0.01), TNF-α ($p$<0.02), IL-2 ($p$<0.003), and IFN-γ ($p$<0.005) from baseline levels in the stimulated PBMC of both groups. Cytokine levels returned to baseline values after a 3-month wash-out period. This study demonstrated the ability of fish oil supplementation to decrease pro-inflammatory cytokines believed to be important in the pathogenesis of MS.

The second was a double-blind placebo-controlled trial in which MS patients ($n$=312) were randomized to receive either 20 capsules of fish oil per day or olive oil capsules for 2 years[68]. This study reported a trend in improvement in the omega-3-treated subjects compared to controls ($p$=0.07). While the results did not achieve statistical significance favoring omega-3 fatty acid supplementation, the study was not optimally designed. Both groups in the study were advised to follow a diet low in animal fat and high in omega-6 fatty acids. Importantly, both groups developed changes in serum fatty acid content over the 2 years of the study. The lack of comparing fish oil supplementation to a placebo oil in patients who did not have other dietary modifications may have affected the ability of the study to detect a statistically significant therapeutic benefit of omega-3 fatty acid supplementation.

### *Parkinson's disease: coenzyme Q10*

Coenzyme Q10 showed a trend towards slower decline in early Parkinson's disease as measured by the Unified Parkinson Disease Rating Scale (UPDRS) over 32 months in 80 subjects while being well tolerated[69], but did not show benefit in a smaller, shorter study in well-established disease[70].

### *Parkinson's disease: broad beans*

L-DOPA was first identified in the seedlings, pods and beans of the broad bean, *Vicia faba* in 1913. In a 1993 study, L-DOPA blood levels were obtained from five healthy volunteers and six patients with Parkinson's disease (mean disease duration of 13 years, stage III HoehnYahr Scale off medication for 12 h) who then ate 250 g of cooked broad beans. Over 4 h, L-DOPA levels were significantly increased and a clinical improvement was noted in the patients[71]. This simple dietary practice may have implications in the treatment of Parkinson's disease.

### *Peripheral neuropathy: γ-linolenic acid (GLA)*

In a 22-patient placebo-controlled study, 360 mg daily of γ-linolenic acid (GLA) showed significant improvement in symptoms, motor conduction velocity, compound muscle and sensory action potential amplitude, and heat and cold threshold in diabetic patients[72]. In a larger study of 111 diabetics over 1 year, changes with GLA were favorable in all 16 measures and significantly favorable in 13 measures[73].

## Homeopathy

Homeopathic medicine was developed about 250 years ago by a German physician, Samuel Hahnemann (1744–1843). The process uses various plants, minerals, or animal products in extremely dilute doses that theoretically in larger doses would cause the symptoms that the patient to whom it is applied is experiencing as a consequence of illness. Hahnemann called this the 'law of similars'. The word 'homeopathy' is derived from the Greek words, *homoios* meaning 'similar,' and *pathos* meaning 'disease'. A homeopath's skill is in matching the substance or remedy to the patient's symptom picture and constitution. Hahnemann viewed disease symptoms as a manifestation of the body's healing systems rather than a breakdown in the body's systems. He believed that the body's process was to be supported and that suppression of symptoms through allopathic drug use would drive the disease deeper into the body, causing more serious chronic physical and mental illness[74]. Each substance used in homeopathic medicine has a unique symptom profile. A simple example would be that of a patient describing symptoms of insomnia, nervous sleeplessness, irritability, heart palpitations or racing heart beat and trembling hands. Large doses of coffee would be a substance that caused these symptoms. Therefore, a homeo-pathic preparation of coffee would be chosen as the remedy for the patient's condition.

Hahnemann recorded these symptom profiles as a response to a given substance by using a systematic method of observation called 'provings'. Hahnemann's first proving was a self-experiment. He took doses of cinchona (a Peruvian bark) which at the time was known to alleviate the symptoms of malaria. After ingesting extracts of cinchona, he came down with intermittent fevers, a characteristic symptom of malaria, providing, by the homeopathic model, both a remedy profile and treatment indication. The following example is used to clarify this model: cinchona (the remedy) induces the symptom of intermittent fevers (a proving) and intermittent fever is one of the signs and symptoms of having malaria. Therefore, cinchona would be one of the remedies indicated for malaria as they both contain the same symptom profile (like cures like). Over the years

Hahnemann compiled ‘provings’ on a number of substances using subjects other than himself. His first book of ‘provings’ included 62 substances (homeopathic ‘remedies’). The symptom picture of remedies ‘proven’ by Hahnemann and others are compiled in various volumes of homeopathic *materia medica* with hundreds of remedy profiles. Although the doses used in the ‘provings’ were at levels that caused physiological symptomology, Hahnemann experimented with decreasing the doses to see how little of a substance could be used to effect a healing response. Hahnemann’s experiences led him to believe that the more dilute a substance became, the better its actions were in stimulating the healing process. He termed the strength of these actions ‘potencies’. The more dilute a remedy is, the more potent its effects are considered to be. Homeopathic remedies are made by making alcohol extracts of plants or crushing mineral substances which are then diluted into specific potencies. Initial potencies may be designated as ‘X’ (1:9 dilution), ‘C’ (1:99 dilution), or ‘M’ (1:999 dilution), which may be further serially diluted, i.e. a 30X is serially diluted 1:9 thirty times resulting in a remedy of which there may be no molecules of the starting substance remaining. After each dilution the remedy is ‘succused’ or shaken. Hahnemann believed that the succusion of the remedy acted to further potentize it. A 6X homeopathic remedy has been diluted 1:9 six times and succused six times and the amount of original substance would be 1 part in 1 million. In a 6C homeopathic remedy the original substance would be diluted 1:99 six times, succused six times, and have one part in a trillion of original substance. The 6C remedy is considered more potent than the 6X remedy. Any remedy that is 24X or 12C or higher would be so dilute that no molecules of the original substance would be found. The remedy can be given in a liquid form taken in water. More often in commercial preparations, the potentized liquid is added to small sugar pills which are taken a few at a time. In general, lower potencies, 1X–12X, 6C, 12C, are used for acute conditions with frequent dosing (every 2–4 h). Higher potencies (30C or greater) are used for chronic conditions and dosed less frequently (from once or twice a day to once a month). Very high potency remedies (200C and higher) are considered ‘constitutional’ and are closely matched to a person’s comprehensive symptom profile and constitution (personality and history). Constitutional prescribing is expected to affect healing at all levels (mental, emotional and physical) and is given very infrequently (once a month or less).

Naturopaths are trained to use homeopathy for acute, chronic, or constitutional conditions. A few naturopaths use homeopathy as their principal treatment for patients; most naturopaths might use homeopathy in conjunction with other therapeutic modalities to stimulate the healing process; some do not use it at all. To date there is no scientific explanation for the mechanism of how homeopathic remedies might act. Although elucidating the mechanism of action of the higher potency homeopathic remedies (24X, 12C or higher) has been a problematic issue, there have been scores of scientific studies evaluating the clinical effects of homeopathy. Several meta-analyses have been performed to determine whether clinical trials in homeopathy show efficacy greater than placebo. Two recent reviews of systematic reviews of homeopathy have reached slightly different conclusions. Ernst conducted a systematic review of clinical trial, meta-analysis and systematic reviews in homeopathy published since 1997 using the following databases: Pubmed, Embase, Amed and CISCOM[75]. From this review he concluded that the efficacy of homeopathic remedies was no better than placebo. Jonas and colleagues have published a comprehensive overview of homeopathy which includes a description

of Hahnemann's philosophy, the history of practice in the USA, FDA regulations and a review of the systematic reviews[76]. The authors concluded that, although there is a lack of conclusive evidence of the effectiveness of homeopathy for most conditions, they held that while 'homeopathy deserves an open-minded opportunity to demonstrate its value by using evidence-based principles…it should not be substituted for proven therapies'. The authors reported that there was evidence from randomized controlled trials that homeopathic remedies may be effective for the treatment of influenza, allergies, postoperative ileus and childhood diarrhea, while it was ineffective for delayed-onset muscle soreness and the prevention of influenza and migraine. Other investigators suggested that the evidence with regard to migraine was inconclusive[77,78].

For other neurological conditions, the evidence for the effectiveness in specific disorders is sparse. A Cochrane review on the efficacy of homeopathy for dementia[79] concluded that there were no studies that fulfilled inclusion criteria (randomized controlled trials with a sample size of 20 or more) for review. Chapman and coworkers[80] performed a randomized, doubleblind, placebo-controlled trial of homeopathy in 60 patients with mild traumatic brain injury (MTBI) showing a trend of improvements in the Difficulty with Situations Scale and the most common symptoms of MTBI. A trial of a homeopathic combination versus betahistine hydrochloride in vertigo showed an equivalence of outcomes[81].

## Physical medicine

Naturopaths are trained in spinal and extremity manipulation (similar to chiropractic and osteopathic manipulation), massage, physiotherapy, electrotherapy and hydrotherapy techniques. These are the interventions of the medical specialty of psychiatry. Hydrotherapy is the use of water to detoxify the body, stimulate a healing response and strengthen the immune system. Colonics, alternating hot and cold applications, and hyperthermal baths are included. There have been few reasonably rigorous trials of the interventions of physical medicine (except for manipulation) other than in post-stroke rehabilitation. Chiropractic manipulation is addressed elsewhere in this book (Chapter 3).

## Psychological counseling

Naturopaths are trained in basic psychological counseling and stress management. Some naturopathic schools offer training in techniques such as biofeedback and visual imaging. The training also includes the importance of issues of spirituality and personal meaning. The most frequent uses of psychospiritual interventions in naturopathic medicine for neurological disorders are related to inducing behavioral changes that are supportive of health. These types of behavioral changes encourage the patient to be more self-empowered about their health by suggesting the use of coping skills that the patient may already have in place (e.g. spiritual practice, prayer) or by introducing interventions that are the patient can easily use on their own (e.g. journaling, deep breathing, short meditation). The physical effects of emotional states are increasingly documented in the literature of psychoneuroimmunology. Still, there are few trials showing effective intervention in most neurological disorders.

## RESEARCH IN NATUROPATHIC MEDICINE: EVIDENCE FOR SAFETY AND EFFICACY

While the scientific literature is thin or equivocal for some of the practices and procedures that characterize naturopathy, over all of the modalities it is substantial. This evidence for naturopathic modalities in neurology is reviewed in part above and more deeply in the various chapters of this book. The lack of definitive research for many of the individual substances and practices is caused in part by the absence of economic incentives, due to their unpatentability as well as by the lack of public funding that conventional biomedicine has enjoyed. The profession is just beginning to develop the cadres of clinical and basic scientists who have contributed so much to the evidence base of conventional medicine. Research is further complicated by the difficulty of working with natural materials that previously were inadequately standardized. There is reliance on treatments, such as dietary change, that are notoriously difficult to control. Many individual naturopathic agents and interventions have relatively small effect sizes in a target disease compared to some pharmaceuticals, and therefore would call for large (and expensive) studies to detect effects.

However, whether practiced as an alternative or a complement, the naturopathic approach does not depend on single agents or modalities. This is also true of other whole systems of practice, such as ayurveda or Chinese medicine. All of these approaches are characterized by treatment through multiple modalities that are individually tailored for each patient's constitution and condition. They often target global outcomes such as vitality, functionality and overall risk reduction rather than specific diseases. Such a whole practice approach is not evaluable in the current gold standard scientific model of the single-agent double-blind randomized placebo-controlled trial with a well-defined disease endpoint, and is difficult to study mechanistically. Even where clinical evidence exists, mechanisms often remain unknown. Thus, the appropriate patients for a particular therapy may be impossible to identify except through therapeutic trial. Fortunately, because of the relatively high safety profile and low cost of many naturopathic treatments, there are lower barriers to therapeutic trials than with some drugs or operations. Combination treatment increases the response rate, as different agents acting by different mechanisms are more likely to find responses in a diverse population presenting with a similar symptom picture. Experimental study of the whole practice of naturopathic medicine with its general approach rather than single substances applied to a specific disease is as vanishingly rare as it is for studies of the entire practice of other nondominant whole systems of practice. Nevertheless, it is in such global study where their true benefit is likely to be found. The absence of such research is partly because the scientific methodologies used to evaluate such systems of medicine are not well established or well accepted[82–86]. Even in conventional medicine, the implicit algorithms of treatment that are the foundation of everyday clinical practice are rarely evaluated in scientific studies. Critical to the proper scientific evaluation of naturopathic medicine is the implementation of study designs that are capable of evaluating a complex approach to treatment which include the characteristics of individualized and multimodality treatments. The situation, however, is beginning to change. With the inception of the National Center for Complementary and Alternative Medicine at the National Institutes of Health (NIH) in 1997 and with subsequent funding and the stimulated interest from

other NIH institutes, scientists and clinicians, scientifically sound methodologies are beginning to be developed and accepted to evaluate the safety and efficacy of holistic systems of medicine[82–85]. This means that an increasing number of studies on the safety and efficacy of such whole systems of practice can be expected in the future.

## RELEVANT WEBSITES

(1) American Association of Naturopathic Physicians (AANP)
www.naturopathic.org
(2) North American Board of Naturopathic Examiners (NABNE) and Naturopathic Physician Licensing Examinations (NPLEX)
www.nabne.org
(3) Accredited Naturopathic Colleges in the USA and Canada
Bastyr University, www.bastyr.edu
National College of Naturopathic Medicine (NCNM), http://www.ncnm.edu/
South West College of Naturopathic Medicine (SCNM), http://www.scnm.edu/
University of Bridgeport College of Naturopathic Medicine, www.bridgeport.edu/naturopathy
Canadian College of Naturopathic Medicine, www.ccnm.edu

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# 8
# Ayurvedic medicine

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*Complementary Therapies in Neurology: An Evidence-Based Approach*
Edited by Barry S.Oken
ISBN 1-84214-200-3 

The term 'ayurveda' can be defined as knowledge *(veda)* of the lifespan *(ayu).* This knowledge is recorded in the ancient literature of India, referred to collectively as the Veda, recently categorized into 40 major groups of texts[1]. Texts traditionally considered part of ayurveda include those of Charaka, Vagbhata, Sushruta, Bhela, Harita and Kashyapa. Collec-tively, they document several approaches to diagnosis, prevention and treatment of disease.

A revival of the understanding of ayurveda in the broader context of Vedic knowledge has been undertaken by Maharishi Mahesh Yogi, who first came to prominence in the West over 40 years ago, with his introduction of the Transcendental Meditation (TM) technique. The technique of meditation is central to ayurveda, and can be considered a cornerstone in building the foundation of a Vedic approach to health.

## THEORETICAL CONSIDERATIONS: THE CONSCIOUSNESS MODEL

A complete understanding of ayurveda first requires an understanding of the purpose of the texts of the Veda, and a comparison of the paradigms underlying the physiology, the physical universe in general and the conscious mind. From the perspective of physics, we understand the scope of the manifest universe to include infinite variety, and that components of this universe range in size from those of galactic proportions to elementary particles. As quantum physicists of the past century delved into finer levels of relative existence, they found that beyond the finest levels of measurable energy—particles, and the forces that govern them—there exists a quantum field, completely unmanifest and beyond measurement. This quantum field is infinite in potential, and the source of all simple and more complex interactions that give rise to the manifest universe. It is the source of the laws that govern the universe, and its orderly evolution.

Human physiology is of course included in this manifest universe, and has underlying it the same absolute, quantum field of infinite potential. As such, it is the source of order in the structure and function of the human organism. Consciousness is considered in our Western allopathic paradigm to be the product of physiology, and in particular of the coordinated functioning of the central nervous system (CNS). Individual consciousness

created as a result of CNS functioning is considered the 'whole which is greater than the sum of its parts', because from measurable finite activity, awareness is created.

The Vedic perspective adds yet another layer to our understanding of consciousness, which serves as a grand unification of our objective scientific observations and our subjective experience of awareness. The central theme of the Vedas is that the unmanifest field underlying the physical universe, including human physiology, the field which we recognize as infinite in its potential, characterized more recently as the quantum field, is the *same* field we call consciousness. This same field gives rise to our awareness, thoughts and actions. In this paradigm, consciousness is not merely the product of the human nervous system but is the source of that system. The unique feature of the human central nervous system is that it is able to experience this unmanifest field at its basis. In so doing, it experiences the fundamental unmanifest field as the basis of the rest of the physical universe as well. For the purpose of clarity, we will refer to this unbounded field experienced on the level of the mind as *Consciousness,* to distinguish it from the usual waking state *consciousness.*

In the Vedic texts, this unmanifest, transcendental field is often referred to as 'atma', a term sometimes translated as 'self' or 'being', 'pure awareness' or 'pure consciousness'. Experiences of this underlying field of pure awareness have been documented throughout the Vedic literature and in both religious and secular literature of numerous cultures throughout recorded history. The experience has been described as one of 'bliss', 'universality', 'being at one with the universe', or 'infinite silence' or 'unboundedness'.

Phrases in the Vedic literature such as 'Aham Brahmasmi' (I am Totality) and 'Ayam Atma Brahm' (This Atma <Self> is Brahm <Totality>) proclaim the experience of pure awareness to be the experience of the true reality of life. Furthermore, the Vedic literature expounds upon the importance of the experience of pure awareness for promotion of health and success in life. An example is found in the often quoted *Bhagavad Gita*[2], from the branch of the Vedic literature termed Itihasa. The main character, Arjuna, faced with the prospect of killing his own kinsmen, is perplexed about what action he should take on the battlefield. He is advised by Lord Krishna: *'Nistraigunyo Bhav Arjun'*—'Be without the three gunas, Arjuna', or in other words, transcend the relative field of activity to arrive at the infinte field of pure consciousness. Lord Krishna also advises: *'Yogasthah Kuru Karmani'*—'Established in Being, perform action'.

## THE TRANSCENDENTAL MEDITATION TECHNIQUE AS A CORNERSTONE OF VEDIC MEDICINE

In practical terms, the means of experience of pure awareness is by a mental technique. The regular experience of pure awareness is a cornerstone of ayurveda, and more specifically of the Vedic approach to health as recently introduced by Maharishi Mahesh Yogi. In recent clinical and scientific literature, it is often referred to as the Maharishi Vedic Approach to Health (MVAH) or Maharishi Vedic Medicine (MVM). The experience of pure awareness is by means of a systematic mental technique, whereby a thought is experienced on finer and finer levels of its inception, until thought itself is transcended, and one is aware, but without an object of awareness. This is the experience of 'pure awareness' or 'pure consciousness'. It is often referred to as the source of

thought or as explained above, the experience of the quantum field on the level of the mind. The technique for transcending thought to arrive at pure awareness is a technique of meditation, specifically, the TM technique. As can be inferred from the explanation above, this is not a technique of contemplation or concentration, but rather a mechanical technique allowing the mind to settle down to its own 'ground state'[3].

The importance of the TM technique in a modern system of ayurveda (MVAH) cannot be overemphasized. It is the cornerstone of Vedic medicine because this mental experience has associated with it profound physiological changes measured both during and after the practice. It is in fact a distinct state of physiological functioning, unlike the waking, dreaming and slow wave sleep states with which we are familiar. Figure 1 summarizes the differ-

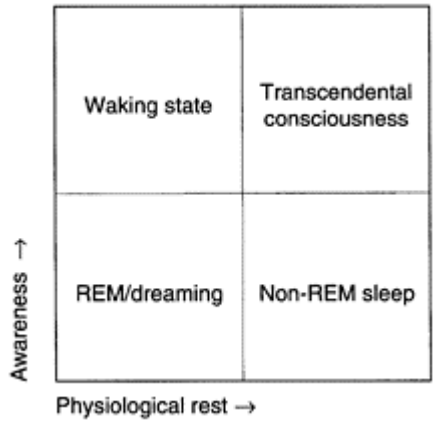


**Figure 1** Four states of consciousness characterized physiologically and by level of alertness. REM, rapid eye movement

ences between the three usual states of consciousness and the fourth state referred to by Wallace as a 'wakeful hypometabolic state', transcendental consciousness, or pure consciousness[3–5].

The state characterized by the TM technique, unlike waking, dreaming and sleeping, is associated with physiological rest with the maintenance of alertness. This alertness is more properly characterized as pure awareness, because while the individual is alert, his awareness is not bound or localized by any particular thought. Through regular practice of this simple technique, one begins to carry over the experience of pure awareness beyond the period of meditation, and into activity. When pure awareness is stabilized physiologically during waking, dreaming and sleeping states, the full mental and physiological potential of the individual has been realized. In Vedic terms, such an individual is said to enjoy perfect health, while enjoying the true blissful nature of the mind, pure awareness, throughout all activity.

## RESEARCH ON THE TRANSCENDENTAL MEDITATION TECHNIQUE

Initial physiological research revealed decreased oxygen consumption and decreased arterial lactate during TM[4], and further research has provided an electroencephalographic (EEG) signature to this state[6–11], with increased alpha power both frontally and posteriorly, and a profound increase in coherence of cortical activity between frontal and parietal regions of the same hemisphere and between corresponding lobes of the left and right hemispheres. Coherence was measured using Fourier transformation of the surface EEG, evaluating the phase and power within narrow frequency bands[12]. This intra- and interhemispheric coherence was the first physiological indication that this simple mental technique could have important consequences for cortical functioning. Specifically, the notion advanced for some time, that the TM technique allowed for a development of mental potential on the basis of a more integrated cortical activity, was supported by this physiological finding[6,13,14].

From a neurological perspective, the importance of the TM technique in disease prevention has been documented in the areas of cardiovascular disease, cerebrovascular disease, atherogenesis and aging of the nervous system. With respect to vascular disease and atherogenesis, there is ample evidence that the TM technique is effective in reducing both elevated systolic and diastolic hypertension, and that this effect is seen even in short-term practitioners of the technique[15–19]. Furthermore, a reduction in carotid intima-media thickness, a surrogate marker for atherosclerosis, has been noted as well[20]. In addition, regular practice of the TM technique has been associated with an increase in exercise tolerance and delay in onset of S-T depression in patients with known coronary artery disease[21].

As stroke is the third leading cause of death in the USA, and the most important cause of morbidity in the elderly, the potential impact of the TM technique on stroke prevention cannot be overemphasized. A longitudinal study of the effect of TM on stroke incidence in a population at risk is appropriate at this time, and the costeffectiveness of this approach and lack of sideeffects are additional reasons why such a study should be undertaken as soon as possible.

The aging of the human nervous system, much like the aging of the entire organism, is considered to have a strong genetic component. However, neuronal loss and white matter ischemic changes can both be accelerated by long-standing hypertension. Thus, the TM technique by virtue of its effect on blood pressure alone is likely to reduce the incidence and severity of these age-related changes, and thereby reduce the incidence of symptomatic dementia and gait disability.

Positive effects of TM on hypercholesterolemia and serum lipid peroxide levels have also been demonstrated[22,23], and a study of biological aging—assessing a composite of physiological and biochemical parameters—revealed that TM practitioners are younger biologically than their non-meditating counterparts[24]. Parameters studied included auditory threshold, near point vision and systolic blood pressure. Added to the above data is evidence of a decrease in the neurotoxic habits of smoking and alcohol abuse, and overall reduction of stress in TM meditators[19,22,25]. Finally, Alexander and colleagues studied the use of the TM technique in the very elderly, and demonstrated an associated

decrease in mortality in this age group, presumably in part as a result of a decrease in vascular events[26,27].

## RASAYANAS AND DISEASE PREVENTION IN THE NERVOUS SYSTEM

In addition to the backbone of Vedic medicine, the technique of TM, other therapeutic techniques and prescriptions described in the Vedic literature are primarily concerned with diet, lifestyle and interaction with the environment. Some of these prescriptions are specific for individuals on the basis of diagnostic techniques described below. Others are considered generally beneficial, irrespective of individual constitutions. Such prescriptions are called rasayanas. One rasayana is an herbal mixture Maharishi Amrit Kalash (MAK), with its main ingredient, amla (Indian gooseberry). MAK has been shown to have potent antioxidant effects *in vitro*[28–30], and inindividuals taking MAK as a dietary supplement[31]. Unlike the TM technique, its effects can be evaluated in laboratory animals.

MAK has a potent free radical scavenging effect, and has been shown to reduce predicted atherosclerotic lesions in rabbits fed an atherogenic diet[30]. There is also evidence that MAK protects low-density lipoprotein (LDL) from free radical attack[31]. In addition, MAK reduced breast carcinoma growth in a murine tumor model[32]. An antineoplastic effect of MAK was also demonstrated in laboratory models of lung carcinoma metastases[33] and skin papilloma. MAK also induced differentiation of neuroblastoma cells in culture[34].

The effects of MAK have also been evaluated in patients receiving standard chemotherapeutic regimens. Overall, a reduction in sideeffects without a loss of efficacy was noted during adriamycin and cisplatin therapies[35].

Both antioxidant and anticarcinogenic effects of MAK are probably related to a synergistic effect of several naturally occurring antioxidants in this herbal mixture. The preparations MAK-4 and MAK-5, an herbal concentrate and tablet, respectively, are composed of over 20 herbs and fruits. By tradition, these are harvested at specified times of the year, which may serve to optimize levels of active phytochemicals and bioflavonoids. Preparation of the herbal ingredients involves grinding to fine powders and processing in the extracts of other herbs. However, ‘active’ compounds are not isolated, as is typically the case in the preparation of allopathic medicines. The ayurvedic literature refers to the ‘wisdom of the whole plant’, allowing for a synergy of the molecular components found in individual herbs, while eliminating the potential sideeffects typically associated with high concentrations of single molecular component drugs.

## BEHAVIORAL RASAYANAS

Just as there are herbal mixtures identified for their health-promoting effects, so too behavioral guidelines are prescribed by ayurveda, to enhance mental health and by implication physical health. Behavioral rasayanas are those behaviors that create a

positive mental state, which via neuropeptidergic and autonomic pathways may enhance immunity. Tracey[36] has recently outlined the importance of the CNS response in the overall response to infection and inflammation.

In the *Charaka Samhita*, listed behavioral rasayanas include: maximizing speech that uplifts people, respect towards teachers and elders, moderation, simplicity, charity, love, compassion and avoidance of anger, harsh or hurtful speech, dishonesty and speaking ill of others behind their backs. Charaka also speaks of knowing the proper time and place for all activities[37.]

## THE DOSHAS IN PHYSIOLOGY

Diagnosis in ayurveda is based on an understanding of the principles underlying human anatomy and physiology as described in the Vedic texts. Specifically, five elements named in the texts as space, air, fire, water and earth are considered to combine to form the three basic principles (or doshas) governing physiology: Vata, Pitta and Kapha (Figure 2). Vata, composed of space and air, is the principal governing motion in physiology. Pitta, composed of fire and water, governs processes of transformation in the physiology. Kapha, composed of water and earth, governs anatomic structure and lubrication.

From an ayurvedic perspective, the balanced activity of Vata, Pitta and Kapha is essential for a normal functioning physiology. Excessive or diminished activity of any of the three doshas may result in disease affecting an organ system or systems. A further elaboration of the panchamahabutas, or five elements of matter, and the three doshas helps elucidate their function in physiology.


**Figure 2** The five elements (mahabhutas) and their relation to the three doshas

Akasha, or space, appears as spaces or pores within the body, from the subtlest level (e.g. spaces maintained with molecular structures) to the grossest level, within and between organs. Vayu, or air/wind, is concerned with aspects of movement in physiology, from the subtlest level of receptor-transmitter interaction and intracellular transport, to the grossest level of circulation and locomotion of the individual. Tejas, or fire, is associated with heat and transformation, and is active in metabolic processes, energy production and consumption, and maintenance of body temperature. Ap (jal), or water, is involved in processes of cohesion and lubrication, and in the maintenance of proper osmolality. Prithivi, the earth element, is associated with form and structure in the body, from molecular and cellular structure to muscular and skeletal development.

Vata, having characteristics of both space and air, governs transport, movement and communication from the subcellular to the organismal level. As such, it is intimately involved in nervous system function, and its derangement is considered a major factor in the etiology of diseases of the nervous system.

Pitta, composed of the fire and water elements, is primarily concerned with functions of metabolism, digestion and transformation, again from the molecular through organismal levels. Kapha, composed of water and earth elements, governs anatomical structure and cohesion.

The three doshas give rise to three types of physiological function, and anatomic structures that display the influence of each dosha. Specifically, Vata gives rise to the shrotas or 'channels' concerned with transportation, communication and movement. Pitta gives rise to the agnis or 'fires' of metabolism, digestion and transformation, and Kapha gives rise to the dhatus or 'tissues' conveying structure and cohesion.

The Vata dosha coordinates movement in physiology, acting through the shrotas, or channels, which are 13 in number, and include the 'channels' anatomically apparent in the respiratory tract, circulatory, digestive and urogenital systems, skin and skeleton. The Pitta dosha acts through the principles of transformation or metabolism, characterized as the 'agnis' or 'fires', also numbering 13. The main agni, jathar agni, is the digestive fire responsible for the initial digestion of food. The 12 other agnis are related to the five major elements discussed above, and the seven tissues or 'dhatus' discussed below.

The Kapha dosha, responsible for structure, acts through the principles which support the tissues of the body. These tissues or 'dhatus' are seven in number, corresponding to the principles upholding chyle; blood; muscle; adipose tissue; bone; bone marrow and nervous system; and reproductive tissues. They are sequentially developed in the order described above, with each step of transformation governed by a corresponding agni.

In ayurvedic terms, health is characterized by fully functioning, balanced doshas, giving rise to unobstructed shrotas, and active, balanced agnis governing the sequential transformation of dhatus, so that all seven are fully expressed. In fact, the basis of the expression of the first dhatu is the formation of 'ojas', a chemical substance as yet not identified specifically by Western science, which is considered the finest product of digestion and the 'essence of the dhatus'[37].

Beyond this general consideration of health is the definition of constitutional type, based on the predominance of the three doshas in the individual's physiology. Certain physical and mental characteristics, likes and dislikes, and 'physiological styles' are typical of one or another dosha predominance. In addition, when one dosha predominates, it is more likely to be found in excess at times, giving rise to disease.

Individuals with a predominantly Vata constitution are of a light build, move quickly, are averse to cold weather, have irregular digestion and light sleep. Those with a Pitta predominance have a moderate build, are averse to hot weather, have a strong digestion, a sharp appetite and sound sleep. Individuals in whom Kapha predominates have a solid, heavier build, act more slowly and methodically, are averse to damp weather, have a slow digestion and heavy, long sleep. For a summary of characteristics, refer to Table 1[37].

As will be noted below under the discussion of prevention and treatment, dietary and other prescriptions are to some extent based on dosha predominance and imbalance. A more comprehensive understanding of the effects of the doshas in the physiology requires an appreciation of sub-doshas of Vata, Pitta and Kapha. These are five named

subdivisions for each of the doshas, related to locations in the body where each dosha exerts its influence[37,38]. As will be discussed later, the first sub-dosha of Vata, prana vata, is responsible for the Vata influence on CNS function.

## PRAGYA APARADH AND THE BASIS OF ILLNESS

The normal functioning of the physiology on the basis of balance of the doshas, the production of ojas, balanced dhatus and agnis and clear shrotas is, from a Vedic perspective, the *normal* state of the physiology. This is the state of human physiology that is able to reflect its infinite, unbounded source, the unified field underlying physiology, which we have previously identified as Consciousness.

Less than perfect functioning of physiology is considered a result of less than perfect expression of Consciousness into matter or, more specifically, human anatomy and physiology. In Vedic terms, we speak of a 'forgetting' of the underlying unity of the unified field, once it has diversified to form human physiology. This 'forgetting' is evident on all levels of physiology, from the molecular level to the conscious level of the mind.

How does this 'forgetting' occur? In the manifestation of human physiology from the unified field, the ability to distinguish and discriminate develops, and is referred to in Vedic terms as the intellect, or 'buddhi'. It is the intellect that loses sight of the unified field and identifies with the ever-changing relative values of physiology instead. This forgetting, referred to as 'pragya aparadh', is considered the primary cause of derangements in physiology leading to disease. These derangements involve the doshas, shrotas, agnis and dhatus, the lack of ojas—the finest product of

**Table 1** Characteristics of individuals in whom one of the doshas predominates

| *Vata* | *Pitta* | *Kapha* |
|---|---|---|
| Light, thin build | Moderate build | Solid, heavier build |
| Acts quickly | Acts with medium speed | Slow, methodical |
| Averse to cold weather | Averse to hot weather | Averse to damp weather |
| Irregular digestive power, irregular appetite | Strong digestion, sharp appetite | Slow digestion, mild appetite |
| Quick to learn | Medium time to learn, medium memory | Slow to learn |
| Quick to forget | Tends to anger | Slow to forget |
| Tendency to worry | Regular elimination | Tranquil, steady |
| Tendency to constipation | Sometimes loose or frequent stools | Regular elimination |
| Vivacious, always moving | Sound sleep, medium length | Heavy, long sleep Stamina, strength |
| Light, interrupted sleep, about 6h | Enterprising, sharp | Dark, full hair |
| Tends to fatigue, less physical stamina | Thin, fair hair | Oily, smooth skin |
| Curly hair more likely | Reddish complexion, moles and freckles | |
| Prominent joints, tendons and veins | Early graying or balding | |
| Dry skin | | |

Reproduced with permission from Elsevier from Sharma HM, Clark C. *Contemporary Ayurueda: Medicine and Research in Maharishi Ayur-Veda.* New York: Churchill-Livingstone, 1998[37]

digestion[39]—and the accumulation of a toxic substance referred to in the Vedic literature as 'ama'.

If pragya aparadh, the mistake of the intellect, allows the physiology to lose sight of the unified field at its basis, and thus entertain disease, then it is logical that a technique that allows for the direct experience of that unified field on the level of consciousness, the TM technique, should stand as the single most important therapeutic technique in Vedic medicine. Whether from an ayurvedic perspective an illness is due to weakened or excessive Vata, Pitta or Kapha, or a derangement of agni, dhatus or shrotas, experience of the unified field should enhance the re-establishment of homeostasis.

The mechanism of the therapeutic effect of the TM technique is intriguing from a neurological perspective. Subjectively, the mind settles down in an effortless manner. As described above, this process is associated with a different mode of cortical functioning, with a distinct EEG signature. It is on the basis of a change in cerebral cortical activity produced by a mental technique that the other physiological effects arise. This is reasonable, given the ability of cerebral cortical activity to govern the remainder of CNS function, including autonomic and neuroendocrine function via the hypothalamus.

## DIAGNOSIS OF DOSHA IMBALANCE

Although the primary cause of disease in Vedic terms is the 'forgetting' of the unified field underlying physiology, in practical terms the manifestation of disease can first be seen as imbalance of the doshas. As discussed above, the Vata, Pitta and Kapha doshas govern aspects of normal physiological functioning. Their derangement can adversely affect those same corresponding aspects of physiological functioning. Vata, associated with motion and transport, can through its derangement be associated with diseases affecting transport. This may manifest as disorders of the respiratory or gastrointestinal systems for example, as motility is central to both. In a similar manner, diseases of the nervous system are often the result of Vata derangement, as movement and transport are central functions of nervous system activity[37]. Pitta in its role governing transformation, and Kapha, in its role governing structure and cohesion, may also be associated with nervous system dysfunction. However, Vata derangement is the most common dosha imbalance in patients with neurological illness.

Diagnosis in ayurveda much as in allopathic medicine involves interviewing the patient (prashanam), visually inspecting the patient (darshanam) and physically examining the patient (sparshanam). The diagnosis of dosha imbalances may be based on the elicitation of symptoms referable to the entire physiology, although the primary manifestation of disease may be in the nervous system. Symptoms of Vata imbalance include anxiety, constipation, fitful sleep or insomnia, cold intolerance and dry skin. Pitta imbalance may manifest as peptic ulcer disease, inflammatory skin conditions, excessive body heat, and anger and irritability. Kapha imbalance may present with excessive sleep, mental dullness, sinus congestion or asthma and obesity[37].

In addition to the elicitation of symptoms by history, signs of dosha imbalance may be evident on visual inspection, as in the evidence of dry skin or motor restlessness indicative of a Vata imbalance. The use of the sense of touch during the physical examination has a special place in ayurveda in the form of the technique of nadi vigyan, or pulse diagnosis. The radial pulse palpated by the examiner is assessed for its quality, in addition to its rate and rhythm.

According to ayurvedic texts, the radial pulse, as palpated progressively proximally to the wrist by the examiner's index, middle and ring fingers, conveys any excessive or diminished influence of Vata, Pitta or Kapha in the physiology at the time of the examination. The theoretical basis for the ability to assess the general state of the physiology by means of palpation of the radial pulse is rooted in the understanding that the cardiovascular system both supplies and receives information from all organ systems. It can thus convey information remotely from organ systems.

Pulse diagnosis is an operator-dependent technique. Its usefulness as part of a more comprehensive Vedic approach to health has been documented, although no well-controlled study of the technique in isolation is available. Pulse diagnosis is an example of a diagnostic technique with a therapeutic effect as well. Attention to the pulse, including the Vata, Pitta and Kapha components, is considered to have a balancing effect on the three doshas. Patients can be taught self pulse diagnosis, both to aid them in diagnosis of dosha imbalance, so that they can alter their diet or daily routine to correct that imbalance, and as a preventive health measure in itself.

## TREATMENT OF NEUROLOGICAL ILLNESSES

The following modalities are employed in the prevention and treatment of diseases of the nervous system:

(1) The TM technique;
(2) Herbal mixtures (rasayanas) as noted in the Vedic literature;
(3) Behavioral rasayanas;
(4) Dietary recommendations;
(5) Daily and seasonal routine recommendations;
(6) Sound, aroma and environmental recommendations;
(7) Purification and elimination therapies.

The effects of the TM technique, herbal and behavioral rasayanas are discussed above. The recommendations for diet, daily and seasonal routines are found in the Vedic literature and vary in part by the diagnosis of dosha predominance and imbalance.

## AYURVEDA AND DIET

With respect to diet, ayurvedic texts enumerate six tastes (rasas) and three main pairs of qualities (gunas) of foods, each with its effect of decreasing (pacifying) or increasing (aggravating) one or more of the doshas. The six tastes are: sweet, salty, sour, pungent, bitter and astringent. In further explanation, breads and rice are considered to have a

sweet taste. A pungent taste is found in hot spices such as pepper. Foods with a bitter taste include green leafy vegetables, and astringent foods include legumes. The three main pairs of qualities of food are: heavy vs. light, cold vs. hot, and oily vs. dry.

A Vata-pacifying diet would favor sweet, sour and salty foods, as well as foods that are warm, heavy and oily. These foods tend to settle the Vata dosha. Foods to be avoided on a Vata-pacifying diet are those characterized by the tastes and qualities opposite to those enumerated above. Specifically, foods that are cold, light, dry, pungent, bitter and astringent tend to aggravate Vata. A Pitta-pacifying diet favors sweet, bitter and astringent foods, and cold, heavy and slightly oily foods. The Kaphapacifying diet favors pungent, bitter and astringent foods, as well as those that are light, dry and warm.

Certain dietary recommendations are considered applicable to all patients, including:

(1) Favoring a lactovegetarian diet;
(2) Eating freshly prepared, well-cooked food;
(3) Avoiding leftovers;
(4) Eating until one feels three-quarters full;
(5) Eating in a settled atmosphere;
(6) Having the main meal at noon;
(7) Including all six tastes in each meal.

## DAILY AND SEASONAL ROUTINES

Daily and seasonal routines are based on the Vedic understanding of the normal variation of the predominance of each dosha over time. The 24-h day is divided into six 4-h segments. Pitta predominates between 10.00 and 14.00 and similarly between 22.00 and 02.00. Kapha predominates between 06.00 and 10.00, and between 18.00 and 22.00. Vata predominates between 14.00 and 18.00, and between 02.00 and 06.00.

As Pitta is concerned with the ‘fire’ of transformation and metabolism, it is logical that it is at its maximum at 12 noon when the sun is highest in the sky. This forms the basis of the recommendation for eating the main meal at that time, when the digestive fire, governed by Pitta, is at its maximum. Similarly, the recommendations for rising and going to sleep are based on dosha predominance during the day. It is recommended that one rise by 06.00, essentially rising with the sun, to avoid rising during the morning Kapha time, associated with some slowness and dullness. One should retire by 22.00, initiating sleep during the evening Kapha time, and avoiding the ‘second wind’ associated with the evening Pitta period.

Other aspects of the daily routine recommended for disease prevention and health promotion include regular elimination in the morning after rising, followed by a warm sesame oil massage (abhyanga), mild stretching exercises (yoga asanas), practice of the TM technique twice daily, moderate exercise, and avoiding both excessive fatigue by overworking and an erratic schedule of eating and sleeping. Seasonal recommendations are governed by the knowledge of the dosha predominance by season. From an ayurvedic perspective, the year is divided into three seasons:

(1) Kapha season from March to June, when the weather is cold and wet;
(2) Pitta season from July to October, when heat is greatest;

(3) Vata season from November to February, when the weather is cold and windy.

In each season, the diet should reflect the need to pacify the corresponding dosha[37].

The human lifespan, much as the day and year, is also divided into intervals during which one or another dosha predominates. Childhood is considered a time of Kapha predominance, and young adulthood a time of Pitta predominance. As we age beyond our middle years, Vata takes over as the predominant dosha. In general, no matter which dosha is predominant, the effects of both the season and time of life may cause additional imbalance. As Vata has a tendency to be present in excess in old age, we expect this time of life to be associated with the corresponding symptoms of dry skin, arthritis (dry joints), constipation and sleep difficulties. The dementias and Parkinsonian disorders are also related to Vata derangement, expressed as improper movement and transport on the molecular and synaptic levels within the CNS, and on the grosser level as derangement in the movements of limbs and ambulation.

The use of sound, aroma and changes in the environment of the individual are somewhat foreign to allopathic medicine, but are considered important parts of the therapeutic armamentarium of Vedic medicine, and are referenced in the Vedic literature. The use of sound is particularly important, and is based on the correspondence between the structure of the Vedic literature and human physiology.

## CORRESPONDENCE OF VEDA AND HUMAN PHYSIOLOGY

An understanding of the expression of human physiology from the unified field is incomplete from a Vedic perspective without an appreciation of the role of the Vedic literature in this scheme. The Vedic texts are considered to be a 'blueprint' of human physiology, and as such are the expression of the laws of nature which find their home in that unified field underlying the physical universe. The relationship between the Veda and human physiology is analogous to the relationship between the full genomic sequence of DNA and the manifest organism on which it is based. The sequential unfolding of matter in general, and of human physiology in particular, from the level of the unified field, starts with the first syllable of Rk Veda. The sequence of this unfolding has been elucidated in some detail.

Working with Maharishi Mahesh Yogi, Dr T.Nader, a neuroscientist and neurologist, brought to light the correspondence between the structure of the Vedas and human anatomy and physiology, with particular reference to the nervous system[1]. This correspondence has been refined in great detail over the past 10 years[40], and has focused not as much on the meaning of individual words in Vedic texts as on their sound value and on the structure of the texts, including arrangements of syllables, words, intervening silences, verses, chapters and divisions. Evaluating the texts in this fashion has led to the discovery of a remarkable one-to-one correspondence between Vedic texts and functional and anatomic groupings within the nervous system.

As an example, the Vedic text known as the Yoga Sutras, ascribed to the Vedic seer Patanjali, corresponds in theme, structure, number and grouping of verses (sutras) to the recognized groups of cortical association fibers. The first of the Vedas, Rk Veda, corresponds in its full complement of verses and structure to the set of all pairs of cranial and spinal nerves.

Just as Vedic texts correspond in structure to different aspects of the nervous system, the sounds which comprise the Vedic texts also show this correspondence. This is the theoretical basis for the practical approaches of Vedic sound, Gandharva Veda and Maharishi Vedic Vibration Therapy (MVVT) as therapeutic modalities of MVM. The vibrational quality of Vedic sound, corresponding to a particular area in the nervous system, can have a localized therapeutic effect in that area. Maharishi Mahesh Yogi described this phenomenon as one of 'resonance'. When one object vibrates, another in the vicinity with the same resonant frequency also vibrates.

The notion of a therapeutic effect of sound, separate from any associated meaning, is not new. We understand that sound can affect the entire physiology on the basis of an initial sensory cortical activation with secondary activation more diffusely in the neocortex, and sequentially in the limbic system, hypothalamus and autonomic nervous system. This effect of sound can be independent of meaning, and be based on sound quality and sequence alone, as is evident for example in the subjective response and objective physiological response we may have to music of different types. In fact, it is the effect of sound on the nervous system that is employed in the TM technique, as a 'mantra' or Vedic sound is experienced on progressively subtler levels of thinking until thought itself is transcended to arrive at the experience of pure consciousness.

The effect of MVVT on symptoms of chronic disease has been reported in a preliminary form, and is encouraging[41,42]. As more patients avail themselves of this technique, further data should be forthcoming.

## OTHER TECHNIQUES IN THE VEDIC APPROACH TO HEALTH

The effect of environmental changes on health promotion and disease prevention is covered in part in the portion of the Vedic literature known as Stapathya Veda. Specific prescriptions are given concerning the orientation of homes and room arrangement within them. Principal among these is the prescription for the front door of a home to face east, with an unobstructed view of the rising sun. The physiological basis for such prescriptions may be rooted in the understanding that direction sensitive neurons have been identified in the thalamus.

Purification therapies, collectively referred to as 'panchakarma', are described in the ayurvedic texts of Charaka and Sushruta. They are often recommended seasonally, and are aimed at reducing the accumulated toxic substance 'ama' as discussed above. These procedures include an initial decrease in fat consumption followed by internal oleation, often with a laxative effect, as well as external oleation[37]. Preliminary research points to a decrease in circulating polyaromatic hydrocarbons, primarily stored in fat, as a result of regular panchakarma therapy[43].

## VEDIC MEDICINE AND SPECIFIC NEUROLOGIC DISORDERS

As discussed above, there is a positive effect of the TM technique, and Vedic herbal preparations including MAK, on cardiovascular and cerebrovascular disease, as noted by studies of the effect of these modalities on hypertension, angina, hypercholesterolemia

and carotid intima-media thickness, and in laboratory models of atherosclerosis and free radical scavenging. These data underscore the usefulness of these modalities as part of a cost-effective strategy for stroke prevention. Studies have already shown the efficacy of the TM technique in reducing overall health-care costs[44–46].

With respect to the management of neurooncological diseases, the data mentioned above concerning the antineoplastic effects of MAK should provide the basis for further research regarding the effects of this and related herbal preparations in models of CNS tumors. In addition, further evaluation of the effects of MAK on the amelioration of chemotherapy side-effects is warranted.

From a Vedic perspective, degenerative diseases of the nervous system are related to Vata derangement, and measures that reduce the excessive influence of Vata in the nervous system may be helpful. These are in general measures that affect the expression of the first Vata sub-dosha, prana vata, or another sub-dosha of Vata which then secondarily affects prana vata.

A more comprehensive approach to treatment of chronic illness, employing the combination of modalities described above, has been studied in individual cases of chronic neurological disorders including Parkinson's disease and multiple sclerosis, with significant improvements in functional outcomes noted[47]. Critical aspects of the interventions described in these case reports included practice of the TM technique, panchakarma techniques, herbal rasayanas and the use of Vedic sounds. A pilot study has also provided evidence of a reduction in carotid atherosclerosis associated with the multimodality approach of MVM along with standard care[48]. Controlled studies comparing this approach to standard allo-pathic care alone should be forthcoming.

Beyond the treatment of neurological illness, MVM and the TM technique in particular show great promise for promoting an ideal state of neurological health. This is underscored by the data on improved psychological well-being, cognition and creativity associated with the practice of TM[13,14,49–54], and the evidence for incorporation of the state of pure awareness in the waking, dreaming and sleep states of consciousness[55,56]. This subjective experience of what has been traditionally referred to as the growth of 'enlightenment' has at last found objective verification.

## CONCLUSION

A Vedic approach to neurological health encompasses the techniques described in the Vedic literature, which allow for the full expression of the unbounded, unified field at the basis of human physiology. This unified field has been identified on the level of the mind as pure consciousness, and the experience of pure consciousness afforded by the TM technique is the cornerstone of Vedic medicine. Techniques of diagnosis and therapeutics prescribed in ayurvedic texts are based on an understanding of the expression of the unified field in the physiology as governed by the doshas Vata, Pitta and Kapha. In addition, an understanding of the Vedic literature as a blueprint for physiology opens the door to the application of Vedic sound as a therapeutic approach to disorders of the nervous system. Well-controlled studies have revealed the usefulness of both the TM technique and ayurvedic herbal preparations for health maintenance in general and for prevention of vascular disease in particular.

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# 9
# Hatha yoga and meditation for neurological conditions

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*Complementary Therapies in Neurology: An Evidence-Based Approach*
Edited by Barry S.Oken
ISBN 1-84214-200-3 

## INTRODUCTION

Hatha yoga and meditation have become increasingly popular in our culture today. The *Yoga Journal* has estimated that almost 15 million people attend or have attended a yoga class and an equal number have tried one form of meditation or another. As these two interconnected disciplines move from their roots as a spiritual practice for personal growth to techniques with potential medical applications, it is worthwhile to evaluate potential mechanisms of action, the evidence for their effectiveness and whether or not they might hold promise in treating patients.

## HATHA YOGA: HISTORY AND THEORY

The potential medical applications of Hatha yoga in the treatment of neurological conditions are linked, in the absence of a clearly defined mechanism of action, to several related hypotheses. One hypothesis is that the postures of Hatha yoga, when integrated with the attention to the breath known as pranayama and practiced in a state of focused or meditative awareness, can modulate or reset the resting tone of the autonomic nervous system either directly or through a modulation of the neuroendocrine system and related neurotransmitters. There are likely to be many more peripheral events that occur in the nervous or musculoskeletal systems that can be measured involving the intrafusal and golgi tendon-organ feedback loops when flexion and extension systems are activated sequentially during the practice of Hatha yoga. Long-time practitioners of Hatha yoga and pranayama have a remarkably sophisticated belief about the motion of the central nervous system during different phases of respiration and this is shared with some doctors of osteopathy. The neuroendocrine-immune system and the autonomic nervous system are felt to be influenced by the motion of the structures of the central nervous system. This motion can be modulated by practitioners of yoga during the practice of Hatha yoga, pranayama and meditation in a similar fashion to other complementary therapies such as some applications of osteopathy.

States of autonomic nervous system imbalance are believed to have a unique relationship to a wide variety of disease processes. Today we live in a society that is infused with a high level of sympathetic nervous system stimulation resulting in an abnormally elevated sympathetic tone. Some of this seems to arise from the pace of the culture, and some from the insecurity produced when the human spirit interacts with an environment that is primarily focused on the material aspects of its own existence. The accepted baseline or 'normal' state of sympathetic tone in our society may be the result of a fundamental imbalance that is unique to our culture. Other states of imbalance are unique to the challenges faced by other societies and cultures. There are also neurologically recognized states of parasympathetic dominance that represent another type of autonomic nervous system imbalance and of course there is a resting tone to the sympathetic and parasympathetic nervous systems that is necessary for health and survival.

Imbalances of the autonomic nervous system and the neuroendocrine axis are present in a variety of acute and chronic diseases, either concomitant with the illness, or as a potential cause of the illness. Essential hypertension is particularly interesting, because in some people a significant component of this illness is a chronic overstimulation of the sympathetic nervous system. What is less clear is whether or not the role of the autonomic nervous system and imbalances in the neuroendocrine system are the cause or effect of the disease, or whether or it not it might represent a basic insecurity in the individual linked with an interaction between the tempo of our times and our state of health.

Hatha yoga is most commonly associated with a series of postures that increase flexibility and reduce stress. What is less well known is that Hatha yoga is a small part of the philosophical system of yoga that originated in India thousands of years ago. The first clear references to the postures of Hatha yoga were in the classic yoga text, *Yoga Sutras,* by Patanjali in 200 BC. The original use of the postures of Hatha yoga seemed designed to prepare the body for meditation and other states of consciousness, all of which were likely to be associated with alterations in the function of the autonomic nervous system. Several texts on Hatha yoga have appeared since the *Yoga sutras* by Patanjali were written, including the *Hatha Yoga Pradipika* by Swatmarama, the *Goraksha Samhita* by Yogi Gorakhnath, the *Gherand Samhita* by Gherand and *Hatharatnavali* by Srinivasabhatta Mahayogindra.

Hatha yoga initially appears to be quite similar to a system of exercise, albeit somewhat unusual. A closer inspection reveals that the postures are integrated with breathing exercises (pranayama), a focused state of attention and awareness, and meditation. Two of the many styles of Hatha yoga that have the potential to be integrated into the treatment of medical conditions are Iyengar yoga associated with B.K.S. Iyengar and Viniyoga associated with T.K.V. Desikachar. Both of these styles of Hatha yoga, as well as Ashtanga yoga, the system of Hatha yoga associated with Pattabhi Jois, lead back to the Hatha yoga master Sri T.Krishnamacharya, and each of these styles of Hatha yoga share many characteristics. The Iyengar system of Hatha yoga is known for its emphasis on technical alignment, Viniyoga is known for its attention to the individualized nature of yoga practice and Ashtanga yoga is known for its vigorous flow in a standardized series of postures. There are of course many other styles of yoga, ranging from Kundalini yoga[1] Sivananda, to Kripalu to integral yoga. Bikram Choudry has recently introduced a

popular yoga system distinguished by the practice of yoga in a very hot room (well over 90°F (32°C)) that is probably not appropriate for most patients, particularly those suffering neurological conditions such as multiple sclerosis. For therapeutic purposes, and particularly since most yoga practitioners do not have medical qualifications, Iyengar yoga and Viniyoga are likely to be best for patients with neurological disorders who would like to begin Hatha yoga. Iyengar yoga has a rigorous certification and recertification process that has been in place for more than 20 years, and there are a number of Iyengar certified teachers throughout the USA.

Balance and alignment, which help to define one's relationship with gravity, is a guiding principle in the practice of Hatha yoga. For example, if you lean forward and hold that position, you may feel fatigue as your body tries to hold the alignment. If you adjust to an erect position you may feel a bit lighter. When the body is in a supported alignment muscles work less and the skeletal system provides a natural system of support. If you lean your body to one side, even by only one or two inches (2–5 cm), and hold that position again, you can feel the muscles on the side you lean away from begin to tense in order to keep you balanced in the field of gravity. Some imbalances come from overuse (use of one side or area in a specific movement that one repeatedly performs at work or sports, or even sleep), some from injuries, while others arise from chronic misuse of the body. For each imbalance, we cultivate a compensatory mechanism that responds to the imbalances to help keep us functioning. Hatha yoga pays close attention to the interplay of imbalances, and compensations that constantly occur within the body, first through the development of awareness of the imbalance. If one shoulder is pulled inwards more than the other, the chest and ribs will have to twist in compensation. This in turn will create subtler compensation further down the body—the pelvis may shift, the knee may have to be adjusted and the ankles may collapse. Each compensatory adjustment is linked, to support the body in relation to gravity. The body is in a state of compromised balance, where the neuromuscular system is constantly working against a subtle (or not so subtle) lean, or twist. Through the practice of the postures of Hatha yoga the intention is to bring the body into an alignment that uses energy more efficiently and triggers a relaxation response in the body. The process of performing the postures or asanas, paying attention to the breath and meditation, cultivates an awareness of subtle asymmetries and relationships that affect our health and ability to move freely, which in turn creates the ability to make a change in alignment.

## CLINICAL EVIDENCE

A search of Pubmed and the Indian scientific medical journals revealed almost 200 clinical trials on Hatha yoga, pranayama and meditation. Many of these publications did not have an adequate description of the methodology used in the clinical trials so that assessing the quality of the research is difficult. Nevertheless, they serve as a useful starting point in beginning to evaluate the potential areas of therapeutic application of Hatha yoga. It has been used and is being used as an adjunctive therapy for a variety of neurological conditions including headaches, essential hypertension, postpolio syndrome, chronic pain and seizures (Table 1)[2–8]. It is also used in the treatment of asthma,

cardiovascular disease, diabetes, mental disorders, osteoarthritis and rheumatoid arthritis, and stress reduction.

A recent randomized trial of yoga and exercise in patients with multiple sclerosis evaluated the effect of yoga and aerobic conditioning on several quality-of-life endpoints: fatigue, cognitive function and mood. Subjects who participated in either a 6-month yoga or exercise class showed improvement in fatigue scores when compared with the control group that was on a 'waiting list' for activity. There was a trend suggesting improvement in mood and there were no statistically significant differences in cognitive function between groups[9].

Latha investigated the use of Hatha yoga for the treatment of headaches in a series of randomized controlled clinical trials and demonstrated a significant reduction in headaches[8], use of medications and perception of stress in the group receiving yoga therapy. Other clinical trials have shown that Hatha yoga may be useful in the treatment of hypertension[5–7,10]. One of these studies found that daily practice of Hatha yoga was as effective as pharmacological agents at reducing blood pressure. Forward bends and inversions, and their modifications, are felt to be particularly beneficial for hypertension. Inversion poses, and in particular headstands, shoulderstands and handstands, should be discussed with a patient's health-care team, since there is a risk of cervical strain, glaucoma and retinal detachment, and aggravation of a variety of medical conditions.

Garfinkel and colleagues (1998) published a study in the *Journal of the American Medical*

**Table 1** Clinical trials in Hatha yoga

| *Diagnosis* | *Reference* | *Type of study* |
|---|---|---|
| Chronic pain (carpal tunnel syndrome) | 2 | randomized clinical trial |
| Chronic pain (osteoarthritis) | 3 | observational study |
| Chronic pain (rheumatoid arthritis) | 4 | controlled clinical trial |
| Hypertension | 5 | uncontrolled clinical trial |
| Hypertension | 6 | prospective clinical trial |
| Hypertension | 7 | randomized, placebocontrolled clinical trial |
| Headaches | 8 | randomized controlled clinical trial |
| Low back pain | Pilot study in progress—Kaiser Permanente and Brad Jacobs, UCSF, San Francisco, CA | controlled clinical trial |
| Postpolio syndome | Pilot study in progress—Conemaugh Health System, Barbara Duryea, Johnstown, PA | controlled clinical trial |

*Association* demonstrating that Hatha yoga was useful in the treatment of carpal tunnel syndrome[2]. In this clinical trial patients with carpal tunnel syndrome were given 11 Hatha yoga postures to perform. The control group was given a splint to augment their current treatment regime; nothing else was added to their treatment. The group treated with the 11 Hatha yoga postures showed significant improvement in grip strength, pain reduction and range of motion. The same authors also evaluated Hatha yoga for pain relief in the treatment of osteoarthritis of the hand[3]. Compared with the control group, the treatment group demonstrated significant improvement with regards to pain, tenderness and range of motion. In another study of patients with rheumatoid arthritis, yoga postures improved the hand grip strength in patients with rheumatoid arthritis and in the control group[4]. Mary Schatz, a physician at Vanderbilt University Medical School, has written *Back Care Basics*[11], a physician's guide to an accessible yoga program for back and neck pain, that has increased the awareness of the medical applications of yoga for musculoskeletal problems. The Arthritis Foundation has suggested that patients suffering from a variety of types of arthritis[12] might benefit from practicing Hatha yoga. There are also group and individualized treatment plans available for the treatment of a wide range of musculoskeletal problems from yoga teachers who have had training in therapeutic yoga, or physical therapists who have integrated yoga into their practices.

The current information from the therapeutic application of Hatha yoga and clinical research is consistent with the hypothesis that one of the primary actions associated with the regular practice of Hatha yoga may be a resetting of the resting tone of the autonomic nervous system and the neuroendocrine axis. In addition, it is a component of the cardiovascular risk reduction programs developed by Ornish and co-workers[13], and others[14]. There are also studies that have shown some reduction of stress, improvement in concentration and increased relaxation in individuals who regularly practice Hatha yoga, pranayama and meditation[15–17].

Pranayama, the yogic science of breathing involving awareness and control of aspects of inhalation and exhalation, as well as the spaces in between, is a sophisticated discipline in itself and an integral part of the regular practice and therapeutic application of yoga. Cultivation of breath awareness, its patterns and the possibilities of using it as a therapeutic fulcrum, is not well-known in Western science. Its deeper importance, however, seems to lie in the way it can train the mind and influence both the neuroendocrine axis and the tone of the autonomic nervous system. In a recent study published in *Human Neurobiology*, Werntz and coworkers measured the alternating dominance of cerebral hemispheric activity that was correlated with increased air flow in the contralateral nostril[18].

## RELAXATION AND RESTORATIVE YOGA

When used therapeutically with patients, the practice of Hatha yoga is often referred to as restorative. Here the poses of Hatha yoga are adapted and modified from the traditional yoga poses, often through the use of props so that some or most of the benefits can be attained by those under stress or suffering from an illness. It is an active form of relaxation. Some of the key features of restorative yoga are an increased attention to a relaxed breath, movement of the spine in all directions, gentle compression and

expansion of the abdominal organs and supported inversions where possible. Restorative yoga can be useful for a wide variety of physical illnesses from headaches to women's health issues to indigestion, and it includes specific sequences of poses for specific medical problems.

## THERAPEUTIC APPLICATIONS OF HATHA YOGA

In addition to the clinical trials involving yoga, there is a rich historical tradition within Hatha yoga of using it to treat various illnesses: arthritis, depression, migraines, strokes and menstrual disorders. For example, B.K.S. Iyengar in *Light on Yoga* mentions a variety of yoga poses that may be useful in the treatment of migraines. These include headstand, shoulderstand, seated and standing forward bends, a seated pose with the soles of the feet together (Baddha Konasana), lotus, breathing exercises and relaxation[19]. Using some of the poses assumes an ability to perform the asanas of Hatha yoga that many people may find challenging. These may need to be adapted depending on an individual patient's limitation. T.K.V. Desikachar has developed a way to prescribe individualized yoga series for patients based on their capabilities and their ayurvedic medical diagnosis. Ayurveda is derived from two Sanskrit words *ayur* and *veda,* which taken together mean 'knowledge of life'. In ayurveda there are three basic universal qualities (satva, raja and tamasic), from which five basic elements are derived: earth, water, fire, air and space. Each person's constitution is made of these five elements. Their interplay is governed by three archetypes or doshas: vata, pitta and kapha. Each person is influenced by an infinite number of possible permutations of these archetypes that govern physiological, mental and emotional aspects of an individual's health and illness. In ayurveda health is in large part determined by the balance of the three doshas; disease is a state that results from external or internal conditions adversely affecting the balance of the doshas.

## MEDITATION

Meditation is most commonly used in the USA in a medical setting as a stress-reduction technique[20]. Although it is an integral part of Hatha yoga, it can be practiced on its own. The focused awareness while practicing the postures, on both the alignment of the body and the movement of the breath, are a meditation within the system of Hatha yoga. In addition most yoga classes begin and/or end with a short meditation and relaxation exercise.

Regular meditation appears to reduce stress and increase relaxation, and like the postures of Hatha yoga it may also improve medical conditions ranging from hypertension to chronic pain through some of the same neurological mechanisms (Table 2)[21–27]. In a recently published study[28], a University of Wisconsin-

**Table 2** Meditation trials in Hatha yoga

| *Diagnosis* | *Reference* | *Type of study* |
|---|---|---|
| Hypertension | 20 | controlled clinical trial |

| | | |
|---|---|---|
| Hypertension | 21 | randomized controlled clinical trial |
| Chronic pain | 22 | observational study |
| Chronic pain (fibromyalgia) | 23 | controlled clinical trial |
| Stress reduction | 19 | controlled clinical trial |
| Stress reduction and anxiety | 24 | observational study |
| Coronary artery disease | 25 | observational study |
| Psoriasis | 26 | controlled clinical trial |

Madison research team has found that 'mindfulness meditation' can produce changes both in the brain and the function of the neuroendocrine system. The findings suggest that meditation may have important biological effects that improve the function of a person's immune system. Even though there are many of styles of meditation, a common denominator is that breathing is frequently used as a technique for increasing concentration. Another point of focus other than the breath is a series of words or phrases known as a mantra. This is a repeated continuously during a meditation session. Meditation sessions vary in length but commonly last 15–45 min. For most patients, it is often helpful to begin with a class or instructions that can be augmented with an audiotape for home use. Consistency of practice, even if it is only for a brief period every day, seems to be an important factor in obtaining benefits from meditation.

## MINDFULNESS-BASED STRESS REDUCTION

Jon Kabat-Zinnt introduced mindfulness-based stress reduction in 1979 as a tool integrating meditation techniques with Hatha yoga at the Stress Reduction Clinic at the University of Massachusetts Medical School. Since this has been taught to many people who are not patients, there are many who have participated without a physician's referral. Since 1979, the 8-week program has treated thousands of patients with a variety of medical conditions, from psoriasis to cancer. It consists of weekly classes and daily practice, integrating meditation, Hatha yoga and a 'body scan' using a series of tapes designed to be used at home. There are clinical research studies using mindfulness-based stress reduction that have shown that it may be useful in patients with anxiety[25], pain , psoriasis and prostate cancer[30] .

## VIPASANA MEDITATION

Vipasana meditation, or mindfulness meditation, comes from the Buddhist meditation tradition and uses breath awareness as the primary point of focus, particularly while beginning. The idea is not to concentrate on any one thing, but impartially to note sensations and thoughts as they arise in the present moment. One then lets them go rather than continuing to dwell on any particular sensation or thought. The state of attachment seems to create a state of agitation and distraction.

## TRANSCENDENTAL MEDITATION

Maharishi Mahesh Yogi introduced this form of meditation to the West. It incorporates the use of a mantra or repeated word or phrase to help focus the mind and increase concentration. Its medical applications have been studied extensively in Iowa at Maharishi University with grant support of the National Center for Complementary and Alternative Medicine at the National Institutes of Health[21,22,26,31–33]. The role of transcendental meditation continues to be evaluated in a variety of clinical research projects and has been used successfully as an adjunctive therapy in the treatment of hypertension, coronary artery disease and stress reduction.

## SIDDHA YOGA MEDITATION

This popular meditation tradition was introduced to the West by Swami Muktananda more than 30 years ago when he moved from India to the USA. In Siddha yoga, the field of awareness during meditation may vary but commonly may begin with the breath and then expand into a more general field of awareness. Chanting is commonly used to support the focus of the mind.

## YOGA, PRANAYAMA, MEDITATION AND HEALTH CARE

Hatha yoga, pranayama and meditation can be adapted for almost any patient. Most group Hatha yoga classes incorporate postures, breathing exercises and relaxation or meditation into a 1–2-h yoga class. It may be a challenge to locate a yoga teacher with the experience and patience to apply yoga therapeutically to a patient, particularly when the teacher may not have a medical background. It is important to remember that few yoga instructors are licensed health-care providers. Many yoga teachers are certified but the certification varies from correspondence courses to weekend training programs to a multi-year process with requirements for anatomy and physiology courses as with Iyengar yoga. It is important to ask teachers about their training and select one who has at least several years of teaching experience and continues to attend yoga teacher workshops. Certified yoga therapists who are experience in teaching Hatha yoga and comfortable working with patients are increasingly common, as Hatha yoga becomes more widely available and integrated with other medical therapies, from the Ornish program for cardiac rehabilitation to postpolio syndrome[33].

It may be useful to recognize that Hatha yoga can be viewed as an exercise system that provides a whole-body work-out or be used restoratively to alleviate fatigue. Medical studies have documented that there are many physical and mental benefits to exercise—improved fat metabolism, weight loss, increased circulation, decreased risk of cancer, to name but a few. Commonly, at any given moment, many of our small blood vessels are constricted, reducing blood flow and supply. During the practice of Hatha yoga the blood supply to these areas and the abdominal organs opens up through compression and expansion. This increased circulation supplies these areas with oxygen and other nutrients as well as improving waste removal. Bone density also increases when periosteal stresses

are placed on the bone, using isometric exercises over a period of time, as occurs with Hatha yoga. It appears to improve co-ordination which will result in fewer injuries, particularly in the elderly. The intensity of yoga practice must be adapted to the individual patient, and in many cases a doctor's supervision may be useful or necessary. This, of course, may limit the usefulness of yoga, given the lack of medical qualifications of yoga teachers combined with the lack of awareness of physicians of how Hatha yoga could be applied in a given illness or condition or what styles of Hatha yoga might be most appropriate for a given patient.

## CONCLUSION

Hatha yoga and meditation appear to be safe and can be used to guide a therapeutic response. Neither Hatha yoga nor meditation is affiliated with any particular religion. This may be of reassurance to some patients, who may have worried that these activities could put them in conflict with their religion. It is important when recommending Hatha yoga and/or meditation for a patient that it be a joint decision based on a variety of factors including the availability of qualified instructors. Some styles of Hatha yoga are quite physically demanding and involve complex series of movements where a trained instructor (and a patient/student with a high level of body awareness) is critical. Meditation, while it does not appear to be as physically demanding, can be challenging, and finding a system of meditation that works for a patient can be problematic. There are many self-instructional materials available—books, videos, CDs—some of which are excellent, particularly for a motivated patient. Hatha yoga and meditation are tools that patients can use to manage their own health and wellness.

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# 10
# Hypnosis

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*Complementary Therapies in Neurology: An Evidence-Based Approach*
Edited by Barry S.Oken
ISBN 1-84214-200-3 

In Woody Allen's film 'The Curse of the Jade Scorpion'[1], two reluctant volunteers are hypnotized at a stage performance and are subsequently commanded to commit daring acts of robbery under the control of the malevolent hypnotist. Across the USA (and, indeed, around the world), hypnosis performers demonstrate the amazing powers of hypnosis by having their participants act foolishly on stage to the delight of the audience—only to 'wake-up' following the show unaware of their actions. Given that these experiences are the closest that most people come to hypnosis and that these familiar notions have been upheld for generations, it is hardly surprising that popular misconceptions about hypnosis still permeate throughout society. A study on the general public's beliefs and opinions about hypnosis[2] showed that a large proportion saw hypnosis as a powerful tool to recover accurate memories, even memories as far back as birth, and many believed things could be done in hypnosis that were not possible while wide awake (e.g. enhanced muscular power). There was also evidence for the continued belief that the hypnotist has control of a person whilst hypnotized. A survey of the preconceptions about hypnosis among preclinical medical students in Australia[3] reported student agreement with statements that a person who is hypnotized will do any thing the hypnotist tells him to and that hypnotic subjects show inevitable amnesia for what went on in hypnosis.

What is the truth about hypnosis? After decades of scientific inquiry, what concepts about hypnosis have stood up to rigorous scientific testing, and how does this compare to the popular view of hypnosis? In an effort to address this, we present an overview of the science and application of hypnosis, with particular focus on both the neurological underpinnings of hypnotic phenomena and how hypnosis can be used as a powerful tool for research and clinical practice. A structure for this knowledge is most effectively supported by first laying the historical foundation. We begin this chapter with a brief chronology of hypnosis starting with the person most often cited as the 'Father of Hypnosis', Franz Anton Mesmer.

## HISTORY OF HYPNOSIS

Conventionally, the starting point for the history of hypnosis begins with Dr Franz Anton Mesmer's discovery and practice of animal magnetism in 1774, although the role of hypnosis in religious and healing practices has been inferred from medical papyri dating back to the Ancient Egyptians. Mesmer's theory of animal magnetism proposed, among other things, that a universal fluid permeated all space and that certain diseases were due to a lack of harmony in the distribution of the flow of this fluid. Although Mesmer's early work incorporated the use of magnets in a similar manner to other healers of the time, he soon proposed that one could distinguish animal magnetism from mineral magnetism and relegated the properties of the latter to a metaphorical framework for the former:

> 'I set forth the nature and action of ANIMAL MAGNETISM and the analogy between its properties and those of the magnet and electricity. I added that all bodies were, like the magnet, capable of communicating this magnetic principle; that this fluid penetrated everything; that it could be stored up and concentrated, like the electric fluid…'[4]

Mesmer's healing practices involved both touching and passing his hands over the bodies of the afflicted, which generated 'restorative crises' involving convulsive seizures. The powerful influence of the mesmerist could be applied to many people at once, and even at great distances or through thick walls. The curative powers of animal magnetism could also be stored and transferred via any object.

Trained at the Vienna Medical School, Mesmer eventually moved to pre-revolutionary Paris where he found his fame and fortune. He was convinced about the importance of his discoveries, and tried for many years in vain to establish recognition from the Royal Society of Medicine, though always on his own terms. Eventually, in 1784, King Louis XVI commissioned a number of scientific luminaries to investigate the claims of animal magnetism. The Royal Commission, which included Benjamin Franklin, Joseph Guillotin and Antoine Lavoisier, elected to test the existence of animal magnetism itself rather than the cures—they argued that its utility could be taken up only after the question of its existence had been answered. A disciple of Mesmer's, Charles D'Eslon, served as the mesmerist for the commission. The commission, after demonstrating that people fell under the influence of animal magnetism when there was none and failing to show any effect when it should have been present, concluded:

> 'Touching, imagination, imitation, these then are the real causes of the effects attributed to this new agent, known under the name Animal Magnetism, to this fluid said to circulate in the body & to spread from individual to individual.'(p. 359)[5]

Thus, the mechanism by which Mesmer claimed to effect cures was discredited by the Royal Commission, giving official support to the growing opposition to mesmerism. Mesmer fell into disrepute. Although some supporters remained, Mesmer's dream of the

adoption of his discovery by the scientific and medical community never became a reality. He died in Germany 30 years later at the age of 81.

The concept of hypnosis involving a crisis seems rather alien to most people today. Hypnosis is more commonly depicted as a sleep-like state in which hypnotized subjects can speak and move about in response to the hypnotist's suggestions. Such views about hypnosis began with the work of one of Mesmer's disciples, Armand Chastenet, Marquis de Puységur. Mesmerism entered a new stage of scientific sophistication, as Puységur shifted focus away from convulsive crises to a condition known as artificial somnambulism. In addition to being able to follow the mesmerist's commands while in this sleep-like state, patients often forgot their experiences when awakened. Although still grounded in the flow of some form of curative fluid, Puységur and his followers believed that the fluid originated in the human body and responded to the mesmerist's willpower. Thus this new theory provided a more psychological approach to the interaction between mesmerist and patient. Puységur documented characteristics of the somnambulistic state including an isolated responsiveness to the magnetizer and a focused concentration on internal mental processes that eliminated external distractions. Now a technique existed which involved commands from the hypnotist, and experimentation led to identification of many of the hypnotic phenomena studied today: catalepsies, amnesias, anesthesias, positive and negative hallucinations, posthypnotic suggestions and individual differences in hypnotic responsiveness. As the claims of mesmerists became more fanciful, involving precognition, somnambulistic medical diagnosis and clairvoyance, scientific investigations were again conducted that led to the official rejection of mesmerism.

The term 'hypnotism' is attributed to the Scottish surgeon James Braid who, in his book *Neurypnology*[6], rejected the mesmerist theories of external influence in favor of a physiological explanation based on neurological exhaustion. The mesmerist's method for inducing the somnambulistic state had shifted from Mesmer's and Puységur's silent touching and stroking to a method of eye fixation. By deliberately fixing attention on a single monotonous stimulus such as a bright object, a special nervous sleep would eventually result. Braid termed this neurohypnotism, from the Greek word *hypnos*, meaning sleep. Braid later shifted his focus from the importance of physiological factors in hypnosis to the importance of psychological factors. He coined the term 'monoideism', meaning a focus on a single idea, and argued that neurohypnotism was just a special case of this more general principle. But the term hypnotism stuck, and thus still carries with it the association of a sleep-like state.

Interest in hypnosis in France was revived in the late 1880s by the neurologist Jean Martin Charcot. Considered by many as the founder of modern neurology, Charcot was an eminent physician at the Salpêtrière Hospital in Paris where he made landmark descriptions of many neurological conditions, including multiple sclerosis and peripheral nerve disorders. Of particular interest to Charcot was a malady known then as hysteria, a disorder expressed by physical and psychological symptoms including delirium, paralysis, rigidity and contraction of muscles, blindness, inability to speak, loss of feeling, and convulsions. Charcot proposed the then revolutionary concept that affected persons suffer from a subtle disease of the brain which is functional rather than due to structural lesions. He noted that response to hypnosis shared many characteristics with hysteric symptomatology, and reasoned that both are expressions of the same

neurological disorder. Hence, he argued that only hysterics were susceptible to hypnosis, since both were based on weak neurological systems. He hypnotized patients in order to induce and study hysterical symptoms, and also made a case for the use of hypnosis as a diagnostic tool: because only hysterics were hypnotizable, one could differentiate hysterically based disorders from those due to structural damage by examining the impact of hypnotic suggestions on the symptoms (e.g. tics). Although many of Charcot's assumptions about hypnosis were later shown to be wrong, the fact that such a prominent figure in medical science was studying it restored credibility to medical hypnosis.

At about the same time that Charcot was promulgating the view of hypnosis as a neurological disorder, two French physicians, Ambroise Liébeault and Hippolyte Bernheim were instead championing the notion of hypnosis as a form of suggestion. Far from the public demonstrations of hypnosis and hysteria at the Salpêtrière, Liébeault and Bernheim were treating the working classes by creating a state of heightened suggestibility followed by direct suggestions for symptom alleviation. Bernheim showed that the entire range of hypnotic phenomena could be elicited in 15% of the normal population and that these responses were not limited to hysterics. The weight of research supported the Bernheim-Liebeault view, and eventually Charcot's disease-based model lost favor.

The work of Charcot and Bernheim was to leave lasting impressions, not least of which was in the development of Sigmund Freud's theories of the unconscious. Freud studied clinical neurology under Charcot and became interested in the notion of hysteria. During his subsequent visits with Liébeault and Bernheim, he witnessed patients' amnesia for suggestions given during hypnosis and saw firsthand how these suggestions, though they remained out of conscious awareness, were able to influence behavior. However, Freud later abandoned the use of hypnosis as a reliable method for gaining access to the unconscious. He described this in *Studies of Hysteria*, written with Josef Breuer in 1895.

After a relative lull in the field of hypnosis, a large-scale research program devoted to the topic was launched by Clark Hull at Yale University in the 1930s[7]. With the contemporaneous development of statistical analysis techniques, Hull was able to take hypnosis research to a new level of sophistication. The therapeutic techniques of hypnosis were further developed during that decade by one of Hull's students, Milton H.Erickson, who advanced the practice and acceptability of hypnosis in clinical practice. By the 1950s and 1960s, surges in hypnosis research had led to methodologically rigorous practices and ongoing development of standardized tools for assessment of the hypnotic response.

## MODERN VIEWS ON THE NATURE OF HYPNOSIS

In spite of the abundance of modern research on the topic, a concise definition of hypnosis still remains elusive. In the view of one prominent researcher[8]:

> '…hypnosis is an altered state of consciousness in which a person has certain imaginative experiences associated with subjective conviction bordering on delusion and experienced involuntariness bordering on

> compulsion. Hypnotized people see things that are not there, they fail to see things that are there, cannot remember what just happened to them, and respond to cues without knowing why. At the same time, hypnosis takes place in the context of a particular social interaction in which the hypnotist gives suggestions and the subject acts on them—an interaction that is embedded in a wider sociocultural matrix of understanding about mind and behavior, including information and misinformation about hypnosis itself.'

This description is a good starting point for a discussion about the nature of hypnosis. Immediately, however, two important qualifiers must be made: first, not all people respond to hypnosis in the same way or to the same extent; and second, there is considerable disagreement amongst researchers as to the central explanation for hypnotic behavior—an issue which is often exacerbated by divergent research methodologies. We will return to these issues a little later, but to begin with it would be instructive to describe the typical hypnotic procedure.

## The hypnotic induction

Ordinarily, a hypnotic procedure involves some form of hypnotic induction followed by suggestions for alterations in sensory, motor, or cognitive experience. Historically, the nature of the induction has changed, but the general principle is that one person (the subject) is given suggestions by another person (the hypnotist) to enter into a hypnotic state. Defining hypnosis as a 'state' has its own complications, which we will address shortly. In Mesmer's time, the hypnotic induction was most frequently unspoken, but entailed touching or 'passes' which eventually produced a convulsive crisis in the subject to effect a cure. Some 60 years later, James Braid's practice of neurohypnotism involved 'throwing the nervous system into a new condition', by having subjects fixate their vision on some object, thus inducing a state of 'nervous sleep'. By the late 1800s, Bernheim had incorporated suggestions for 'sleep' into the hypnotic induction, while generally still maintaining eye fixation techniques or having the subject visually track the hypnotist's gesturing fingers. Today, the hypnotic induction typically incorporates suggestions for relaxation, sleepiness and going deeper into hypnosis. However, research has demonstrated that active/alert forms of hypnotic induction can be used successfully, even with participants riding stationary bicycles[9,10]. Such historical transitions and current disparities in the nature of the hypnotic induction have caused some to question its necessity in eliciting subsequent hypnotic behavior[11]. However, most researchers and clinicians still argue for its utility.

## Hypnotic suggestions

Immediately following the hypnotic induction, specific suggestions are given by the hypnotist. Suggestions can be conveniently categorized into ideomotor, challenge and cognitive suggestions. Ideomotor suggestions involve direct suggestions for physical movement. For example, the hypnotist may suggest that the subject's arm, held out in front of them, is becoming increasingly light and rising like a balloon filled with helium,

or that the subject's hands, held out about a foot apart, are being drawn toward each other until they touch. Challenge suggestions are for the inhibition of some motor response. A subject may be told that his or her arm is becoming stiff, like a bar of iron, and then challenged to try to bend the arm. Or they may be instructed that their eyelids will feel glued shut and that they will be unable to open their eyes, and subsequently asked to try to open their eyes. Cognitive suggestions cover a wider range of phenomena. Suggestions may involve auditory or visual hallucinations such as hearing a fly buzzing around the participant's head or seeing a cat sitting in their lap. They may involve suggestions for age regression, memory impairment, alterations in the perception of smell or taste, or even an inability to state the name or function of a common household object such as a pair of scissors. Suggestions may also be given for alterations in physiology, such as decreased blood flow, improved healing of wounds, or even suggestions for increases in immune functioning. Though perhaps more controversial, these latter suggestions have the advantage that subsequent responses cannot be readily faked.

Under hypnosis, subjects do not act as passive automatons but instead are active problem solvers who incorporate their moral and cultural ideas into their behavior while remaining exquisitely responsive to the expectations expressed by the experimenter. Nevertheless, the subject does not experience hypnotically suggested behavior as something that is actively achieved. To the contrary, it is typically deemed as effortless—as something that just happens. People who have been hypnotized often say things like 'My hand became heavy and moved down by itself' or 'Suddenly I found myself feeling no pain'. Many researchers now believe that these types of disconnections are at the heart of hypnosis.

## Individual differences in hypnotic responsiveness

Not all people respond to hypnosis in the same way or to the same degree. The observation that people differ in their general level of responsiveness to hypnotic procedures dates back to the work of Braid[6] and Bernheim[12]. By the late 1950s, standardized scales for assessing hypnotic responsiveness (alternatively termed hypnotic suggestibility, hypnotizability, hypnotic susceptibility) had been developed, scaled and normed[13]. Two of the most widely used scales for hypnosis research are the Harvard Group Scale of Hypnotic Susceptibility, Form A (HGSHS:A)[14] and the individually administered Stanford Hypnotic Susceptibility Scale, Form C (SHSS:C)[15]. The use of these standardized scales ensures that each subject receives the same hypnotic induction and the same set of suggestions. Each suggestion calls for an observable response and thus each suggestion will be passed or failed by the subject according to predetermined objective criteria. An individual's hypnotic ability can thus be quantified according to the number of suggestions that he or she passes, and thus this responsiveness may range from high to negligible. The psychometric properties of the standardized scales provide researchers with an approximately normal distribution of scores (Figure 1). Criteria are usually established for research purposes; for example, groups are divided into high (score 8–12), medium (score

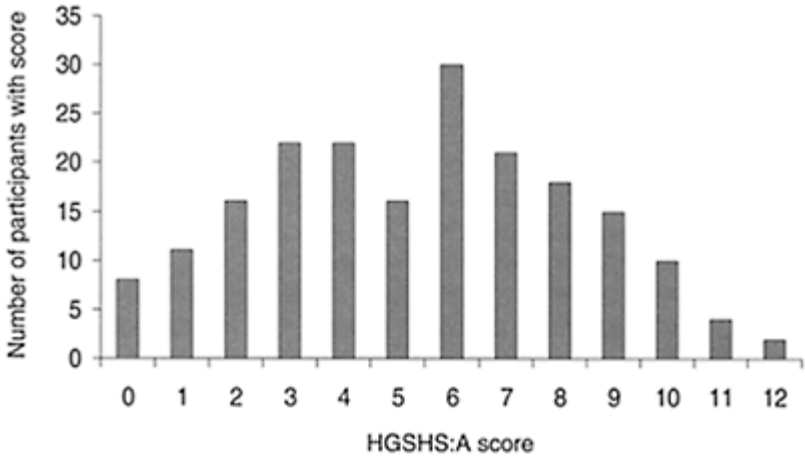


Figure 1. Sample distribution of individual hypnotizability scores of 196 participants (unpublished data). HGSHS:A, Harvard Group Scale of Hypnotic Susceptibility, Form A

5–7), or low (score 0–4). That is not to say that overt behavior is the be-all and end-all of hypnotic responsiveness; the scales are founded on the assumption that these objective responses are reliable markers of subjective experience. An individual's hypnotic responsiveness also appears to be relatively consistent over time and context. A long-term follow-up study in which subjects were readministered the SHSS: A, 10–25 years after it was first administered, demonstrated an overall test-retest reliability of 0.71[16]. This kind of stability compares favorably with test-retest reliabilities for IQ tests over similar periods of time. Interestingly, our own archival analysis of data from the past 40 years has shown a steady overall increase in average hypnotizability scores as assessed by both the group administered HGSHS:A and the individually administered SHSS:C[17].

Standardized assessments of hypnotic responsiveness are important not only to researchers, but also to clinicians. There is evidence that, for certain conditions, such as pain, an individual's hypnotizability is reliably associated with his or her responsiveness to hypnotic treatment. For decades, clinicians and researchers alike have attempted to predict hypnotic responsiveness by means of demographic and personality variables such as sex, age, extraversion, gullibility, compliance, or creativity. Though there is some indication that females might score higher than males on measures of hypnotizability[18,19], and that hypnotizability peaks in children at around 9–13 years of age[20,21], the search for a strong relationship between hypnotic ability and personality constructs has been relatively unsuccessful. Perhaps the most reliable correlate of hypnotizability involves 'absorption'—the propensity for having episodes of all-encompassing involvement toward attentional objects, such as losing oneself in a good novel to the exclusion of external stimuli. Absorption has commonly been assessed by the Tellegen Absorption Scale[22] (TAS). However, at best, the association between these two measures is quite

small, roughly 0.3. Thus, the dilemma remains: the only real way to assess how well someone will respond to hypnosis is to hypnotize them and see how well they respond. Freud addressed this in 1891, when he wrote: 'We can never tell in advance whether it will be possible to hypnotize a patient or not, and the only way we have of discovering is by the attempt itself'[23]. Because scales such as the SHSS:C and the HGSHS:A can take over an hour to administer, faster measures of hypnotic ability have been devised for clinical assessment, such as the Stanford Hypnotic Clinical Scale[24], which requires approximately 20 min to complete.

## Explaining individual differences

One way of understanding these individual differences in hypnotizability is to assume that they reflect essential differences in trait-like cognitive ability[25–27]. According to the trait view of hypnosis, people vary (roughly normally) in their capacity for experiencing hypnosis; individual differences in response to hypnosis are then simply a reflection of people's differing hypnotic ability. Support for this view comes from twin studies which show a significant heritability index for hypnotizability[28]. A contrasting explanation of these differences, the sociocognitive perspective, is that an individual's attitudes, expectations and motivations regarding hypnosis, coupled with contextual factors surrounding the hypnotic procedure, shape his or her responses to various hypnotic suggestions. Thus, hypnotic responsiveness is primarily a product of culturally mediated attitudes and expectations which render the individual either more, or less, likely to enact the role of hypnotic subject. An especially strong version of the expectancy theory[29] argues that expectations are possibly the most important determinant of hypnotic responding. Kirsch has suggested that 'it is possible that, with sufficiently strong response expectancies, *all* individuals would show high levels of hypnotic response'[29]. In an influential article indexing the effects of various expectancy manipulations on subsequent hypnotic susceptibility scores Wickless and Kirsch[30] gave subjects false feedback which was designed to 'fool' them into believing they were good hypnotic responders. The results indicated that subjects who had been given this 'bogus' feedback to increase their expectations scored higher on a subsequent standardized scale of hypnotic susceptibility. The authors interpreted their findings as supporting the notion that hypnotic susceptibility is primarily determined by response expectancy prior to and during the initial hypnosis experience. However, the results of two separate studies conducted in our own laboratory failed to replicate these findings[31]. Even after having demonstrated a significant increase in subjects' expectations, we found no effect on actual hypnotic behavior or subjective experience. In other words, the manipulation of response expectancy had no measurable effect on hypnotic responsiveness. This is not to say that expectancies play no role in determining the quality of hypnotic response, or that clinical patients might not benefit from a preliminary training or instruction procedure[32], just as new psychotherapy patients benefit from preliminary information about the nature of psychotherapy[33].

Sociocognitive theorists commonly see hypnosis not as a function of altered mental states, but as a complex social interaction influenced by expectations, motivations and social demands. They support this position by demonstrating that many hypnotic responses can be elicited without the use of an induction. With the development of brain

imaging techniques, researchers have increasingly been interested in demonstrating neurological signatures for hypnosis as an altered state. It is to this issue that we now turn.

## HYPNOSIS AND THE BRAIN

With the advent of the electroencephalogram (EEG) in the 1920s, researchers soon had a tool with which to measure hypnosis-related changes in the cortical activity of the brain. More recent development of brain imaging techniques such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) have led to exciting new avenues of research related to hypnosis and the brain. In studying the physiological substrates of hypnosis, there are three main lines of attack. The first, following Braid's early views of *neurohypnotism* or Pavlov's views of hypnosis as a state of cortical inhibition[34], is to identify the physiological signature of the theorized hypnotic state. The second, perhaps more in line with Charcot, is to demonstrate baseline differences between people of varying hypnotic ability, that is, to show that the *capacity* for responding to hypnotic suggestions is reflected in the brain even before hypnosis. Some have argued that hypnosis is not a cohesive state, that at any moment a subject may be experiencing a direct motor suggestion, a challenge suggestion, a suggestion for a positive or negative hallucination, or perhaps amnesia. As Kihlstrom states[8], 'Each of these hypnotic activities and experiences is likely to be mediated by a different brain module or system, and it is not clear that they will have anything in common.' The third line of attack focuses on specific changes in brain functioning that result from individual suggestions under hypnosis, i.e. neural correlates of hypnosis dependent on what the hypnotized subject is doing.

### Brain activity changes associated with the state of hypnosis

If, as many researchers believe, the hypnotic induction produces a readiness to accept and respond to hypnotic suggestions, one should be able to observe changes in brain activity from the waking state as a result of the hypnotic induction. Given the historical and behavioral associations between hypnosis and sleep, researchers initially tried to demonstrate similarities between sleep and hypnosis EEG recordings[35]. After many unsuccessful attempts, researchers began to look for distinguishable traces in the various EEG bandwidths that would differentiate hypnosis from the waking state. Research on this topic has been continuing ever since, although consistent findings remain ephemeral. For some time, researchers associated increased alpha activity (8–13 Hz) with hypnosis, but later reviews showed methodological problems with many of these initial studies[36]. More recent work has focused on the EEG frequency band known as theta (3–7.5 Hz), demonstrating increased theta power during hypnosis as compared to prehypnosis baseline conditions[37]. Although there is some additional evidence for increased delta (1.5–4.0 Hz) during hypnosis, this may be associated with hypnotic relaxation[38]. Though less common, some researchers have successfully differentiated hypnosis from the waking state through PET techniques[39,40]. Results from this line of research have shown that changes in regional cerebral blood flow (rCBF) in sensory and motor cortical areas,

the anterior cingulated cortex (ACC), brainstem and thalamus contribute to the experience of being hypnotized.

### Brain activity differences associated with hypnotic ability

With improved measures of hypnotic responsiveness, researchers have increasingly favored examinations of the relationship between brain functioning and hypnotizability. Thus, rather than attempting to identify qualitative and quantitative shifts in brain activity as a result of the hypnotic state, they have focused on demonstrating differences in brain activity between subjects of varying levels of hypnotic susceptibility. A number of recent studies[41–43], have demonstrated a strong connection between hypnotic susceptibility and EEG theta activity, in that outside of hypnosis 'high hypnotizables' show substantially greater mean theta power than 'low hypnotizables', with data pointing to larger EEG theta differences in the more frontal areas of the cortex. It is argued that this elevated theta activity may reflect the high hypnotizable participant's ability to narrowly focus attention and ignore competing stimuli[44].

### Brain activity associated with responses to specific hypnotic suggestions

The phenomenon of hypnosis is most powerfully demonstrated by subjects' responses to specific suggestions during hypnosis. In light of this, it has been argued that brain imaging studies of hypnosis should focus less on the state of hypnosis as a whole and more on the examination of physiological changes associated with specific hypnotic suggestions[8]. In one such study investigating hypnotically suggested positive auditory hallucinations, researchers demonstrated that, when subjects heard a sentence or hypnotically hallucinated hearing the sentence, their brain activity was quite different from that during quiet baseline or when simply imagining the words being spoken[45]. PET scans were used to measure changes in cerebral blood flow as subjects listened to a taped message that read 'The man did not speak often but when he did, it was worth hearing what he had to say.' For the imagination condition, subjects were instructed to imagine 'as vividly as possible, hearing the same man's voice repeating the phrase over and over again', and for the hallucinating condition they were again instructed to listen to the taped message, but the tape recorder was not played. As subjects heard the real recording, and during the hypnotic hallucination of the recorded message, increased activation of a region in the right anterior cingulate was shown. Additionally, subjective ratings of the vividness of the hallucination ('clarity') and the extent to which the voice was experienced as coming from outside of their head ('externality') were strongly correlated with the rCBF response ($r$=0.85 and $r$=0.95, respectively). One additional finding from this study should be noted: high hypnotizables who could readily hallucinate showed quite a different brain profile from equally high hypnotizables who were not good at hallucinating, thus adding support to the notion that hypnosis is not 'just one thing'.

Other PET-based research[46] has examined the brain processes involved in hypnotic visual hallucinations. Highly hypnotizable subjects were presented with a colored and a gray-scale pattern. Activity in the fusiform/lingual region (related to the perception of color) was shown when subjects were asked simply to perceive color as color versus

when they were asked to perceive gray as gray. But, incredibly, when subjects were hypnotized, both the left and right hemisphere color areas were activated when they were asked to perceive color, regardless of whether they were actually shown the color or the gray-scale stimulus. What is more, subjects showed decreased activity in this same brain region when they were told to see gray-scale, regardless of whether they were actually shown the color or gray-scale stimulus.

There is further evidence from EEG studies utilizing event-related potentials (ERPs) that changes in brain activity accompany the experience of hypnotic hallucinations. ERPs are EEG recordings that are time-locked to a series of perceptual stimuli, thus providing a certain level of temporal resolution in brain imaging studies and, unlike standard EEG studies which assign specific frequency bands (e.g. theta) to generalized hypnotic responding, studies using ERPs are less influenced by contextual factors such as happy or sad mood states[47]. The amplitude of cortical activity seen 200–500 ms after presentation of a stimulus are considered to be related to factors such as perception of the stimulus, the degree to which the stimulus is unexpected[48] and the extent to which the stimulus is consciously perceived[49]. When suggestions for visual hallucinations were given to highly hypnotizable subjects, the normal ERPs occurring 300 ms after the stimulus ($P_{300}$) were shown to be attenuated if the suggestions called for hallucination of an obstruction to the stimulus (a positive hallucination)[50,51]. Thus, byreducing the perception of the stimulus because of a hypnotically suggested visual obstruction, the normally demonstrated ERPs were suppressed. However, negative obliterating instructions (a suggestion not to perceive the stimuli) actually produced *greater* ERP amplitudes[51,52], demonstrating the specificity of neurophysiological responses to closely related hypnotic suggestions.

Much work in hypnosis has been directed towards reducing pain through hypnotic suggestions, and there are a number of recent investigations examining the associated changes in brain activity. In one ingenious study, subjects were presented with a hypnotic intervention to change the distress associated with pain rather than the perception of pain itself[53]. By administering suggestions for increased or decreased unpleasantness of the pain, rCBF changes were shown in the anterior cingulate but not in the primary association cortex. A follow-up study[54] involved suggestions for decreasing or increasing the pain *intensity* associated with the immersion of subjects' hands in painfully hot water. Direct comparison of rCBF during the two suggestion conditions (increased vs. decreased pain intensity) demonstrated significant differences in the somatosensory cortex, but no significant differences in the ACC. The results of these two PET studies are shown in Color Plate 1. The authors concluded that their work demonstrated '…a double dissociation of cortical activity related to the perception of pain intensity and pain affect within somatosensory cortices and ACC, respectively'[54]. The PET studies just described outlined the neurophysiological correlates of suggestions for hypnotic analgesia and altered emotional appraisal of pain. With this in mind, we now turn to general evidence for the efficacy of hypnosis in clinical interventions, especially its usefulness in the control of pain.

## THE STATUS OF HYPNOSIS AS AN EMPIRICALLY VALIDATED CLINICAL INTERVENTION

Probably no contemporary therapeutic intervention has a longer history than that of hypnosis. In a recent special issue of the leading journal of hypnosis research, *The International Journal of Clinical and Experimental Hypnosis*, evidence for the efficacy of hypnosis in clinical treatment was critically examined following the guidelines advanced by Chambless and Hollon for empirically supported therapies[55]. The arena in which hypnosis has probably proved itself most adequately is that of hypnotically induced analgesia, providing reduction of both chronic (e.g. cancer) and acute (e.g. painful medical procedure) pain[56]. Hypnotic analgesia has a long history, with prominent figures such as the Scottish surgeon James Esdaile (1808–59) demonstrating its apparent effectiveness for surgery (including 200 patients with massive scrotal tumors) during his time in India. The fervor surrounding this particular use of hypnosis declined shortly after the completion of Esdaile's work, however, with discovery of the anesthetic qualities of ether and chloroform in the mid-1840s. Beginning around 1930, interest in the reduction of pain by hypnosis resumed and today, from burn wound debridement[57,58] to childbirth[59] to bone marrow aspirations[60] and cancer in children[61], hypnosis has found recognition as a dramatic method of producing analgesia which in some cases has matched or exceeded that derived from morphine. Additionally, research with naloxone, a drug that acts as a competitive antagonist at the opioid receptor, shows that hypnotic analgesia is not mediated by endogenous pain mechanisms involving endorphins[62]. A 1996 National Institutes of Health report[63] found 'strong evidence for the use of hypnosis in alleviating the pain associated with cancer' (p. 313) and other data 'suggesting the effectiveness of hypnosis in other chronic pain conditions, which include irritable bowel syndrome, oral mucositis, temporomandibular disorders and tension headaches' (p. 315). A meta-analysis of studies of hypnotically suggested pain reduction, based on pain reports from 933 participants, showed that such suggestions provide substantial pain relief for 75% of the population across different types of experienced pain[64]. In one of the included studies, self-hypnotic techniques were used during interventional radiological procedures[65], in which intravenous pain medication was self-administered by patients by means of a push-button automated delivery system. Compared to hypnosis patients, the control patients as a whole used seven times more drug units and reported significantly more maximal pain. Not only was the pain reduction evidenced by subjective reports and behavioral response, but the reduction of drug use in the hypnosis group was associated with a significantly lower incidence of oxygen desaturation and significantly fewer procedural interruptions due to cardiopulmonary instability. Other research has shown that pain typically increases over the course of percutaneous medical procedures, but remains stable for patients using *self*-hypnosis techniques[66]. However, the efficacy of self–hypnosis tech– niques is not assured. A recent investigation found hypnotic intervention to be effective in the reduction of pain, anxiety and distress behavior in children undergoing lumbar puncture procedures, but only when heterohypnosis (therapist-administered hypnosis) was used, not when children used self-hypnosis[61]. It is clear that future research will need to address such disparities. For those interested in examining this topic further, a recent review of

review articles that deal in some fashion with hypnosis and pain[67] provides an impressive preliminary resource.

Reviews of the literature[68–71] illustrate the diversity of physiological conditions that have been treated and investigated by hypnosis researchers and clinicians. Burns[72], allergic reactions[73], skin temperature[74], blood pressure[75], asthma[76,77], dermatological disorders (e.g. warts[78–80]) have all reportedly proved mutable via hypnotic suggestions. Hypnosis was used in several of the earliest studies exploring the ability of a psychological intervention to affect immunological reactivity[81,82]. However, in spite of the large amount of literature supporting the efficacy of hypnosis in treating a variety of immune-related disorders[83], there still remains a scarcity of solid experimental evidence demonstrating that the immune system is responsive to hypnotic suggestion. Additionally, many of the studies that examine the potential for hypnosis to influence immune functioning fail to control for the effects of relaxation[84], a technique capable of modulating the immune system[85]. However, there have been a few studies that have examined this issue more carefully, either by utilizing measures of hypnotizability as a subject variable[86] or by directly controlling for relaxation[87]. In one study of direct hypnotic suggestion[87], subjects were given the suggestion to 'imagine your white blood cells attacking and destroying germ cells in your body', a suggestion that they used during self-hypnosis for the following week. Subjects in a relaxation group participated in flotation restricted environmental stimulation therapy (REST) sessions, in which they floated effortlessly in a solution of Epsom salts in a fiberglass tank. Analysis of blood samples showed significant immunomodulation for subjects given hypnotic suggestions, based on B-cell and T-cell counts, but not for subjects who received just relaxation. A study involving children also showed increases in immune functioning as a result of hypnotic suggestions, this time in an immune component found in the saliva, secretory immunoglobulin A (sIgA)[88]. However, the clinical implications of such increases are limited. For example, although one would implicitly assume that increasing immunoglubulins is a'good thing', research on the effects of acute physical and mental stress have shown similar *increases* in sIgA levels. Investigations from our own laboratory have suggested that the physiological mechanisms involved in the sIgA increases may differ between the two tasks (acute stress and hypnosis), but the results also demonstrate that increases in sIgA following hypnotic suggestions may be short-lived. Thus, the clinical relevance of hypnotic immunomodulation will be suitably assessed only after long-term outcome studies have demonstrated its impact on health.

In the realm of neuromuscular and neurological disorders, hypnosis has been reported as an effective adjunctive treatment for organic brain damage[89], Parkinson's disease[90], stroke[91], peripheral nerve lesions[92], cases of organic paralysis[93], various types of dystonia[94,95] and multiple sclerosis[96]. These reports, based on case studies with individual patients, provide a first step in demonstrating the usefulness of integrating hypnotherapeutic procedures into treatment of neurological conditions. For example, with multiple sclerosis, various symptoms have been ameliorated via hypnosis, including spasticity[97,98] and multiple sclerosisassociated pain[99]. Such case studies shed little light on the underlying means of improvement and, perhaps more importantly, do not control adequately for any treatment effects due to increased motivation, attention, or relaxation. Nevertheless, with repeated reports of success, there seems good reason for further examination of the application of hypnosis to such disorders.

In spite of their drawbacks, case studies have served the field of hypnosis well, consistently supplying a rich supplement to empirical research and frequently acting as the catalyst for later experimentation. The most famous case of the use of hypnosis in treating dermatological conditions was a report by the physician A.A.Mason of his treatment of a patient with congenital ichthyosiform erythroderma of Brocq (fish skin disease)[100]. The report, which appeared in the *British Medical Journal* in 1955, detailed the dramatic removal of the patient's thick, scaly, inflexible skin as it softened and fell off following hypnotic suggestions. Although carefully controlled studies are not viable owing to the relatively infrequent occurrence of this particular condition, similar results were obtained by two subsequent medical practitioners[101,102]. The role of hypnosis in dermatology has more commonly been demonstrated in the alleviation of warts[78–80]. In one study[78], those who received hypnotic suggestions for wart removal demonstrated a 50% cure rate (as assessed by the number of warts lost and the percentage of wart loss at a 6-week follow-up). This was significantly higher than the rate achieved by participants who had been assigned to a waiting list control or who had received a cold laser placebo treatment. There have been a number of reviews supporting the potential for hypnosis to treat dermatological disorders[103]. With increasingly rigorous studies, researchers are beginning to identify the specific variables associated with successful outcome, but there is insufficient information at present to confidently assert that the positive results are due exclusively to hypnosis[104].

Given that hypnotic interventions are often used as a component of a more complex treatment and that certain studies use hypnotic techniques that are not explicitly defined as such[105], a clear picture has not yet emerged as to the importance of hypnosis as a primary component in successful medical treatment. However, with the encouraging preliminary results of well-designed studies, researchers remain optimistic about demonstrating the usefulness of hypnotic techniques above and beyond that of other psychological interventions. Alongside these efforts at validating efficacy, future research will have to elucidate the mechanism by which verbal suggestions during hypnosis might affect physiological changes.

## HYPNOSIS AS A RESEARCH TOOL

We have presented hypnosis both as a tool for affecting change and as a phenomenon in its own right, including the psychological and physiological components of that phenomenon. Many have argued for the importance of hypnosis as a research tool—a tool to examine cognitive functioning of normal and pathological conditions—by inducing certain mental states in healthy subjects. As Ernest Hilgard stated many years ago[106]:

> 'If hypnotic investigators are successful in what they are doing, they should be able to tell us not only about hypnosis but about human functioning more generally and so contribute to the understanding of normal consciousness and the control systems affecting it.' (p. 138)

The potential for hypnosis to enhance studies in cognitive neuroscience is readily apparent with such active and specific manipulation of attention, perception, memory, and consciousness. In studies of attention, the Stroop Interference Effect (SIE) is used to demonstrate the difficulty that most individuals have resisting the automatic processing of a word's meaning when it is presented to them. If asked to name the ink color of a color word, people are usually much slower and less accurate if that word is printed in a color that is incongruent with the 'meaning' of the typed-out word (e.g. the word 'RED' printed in blue ink). Research has challenged conventional models of automatic and obligatory word recognition, by demonstrating reduced SIE when individuals are given suggestions to see the presented words as meaningless characters of a foreign language[107]. Such effects are not due to simple eye defocusing, and research is slowly identifying the specific brain regions involved in hypnotic inhibition of the Stroop effect[108]. The use of hypnosis in memory research has aided in the examination of the constructive and reconstructive nature of memories[109,110] and the nature, structure and function of autobiographical memories[111]. Researchers have also investigated conditions such as conversion hysteria by generating symptoms in healthy subjects using hypnosis. In a single-case PET scan study in which a hypnotized subject was given suggestions for left-leg paralysis[112], the resultant hypnotic paralysis activated similar brain areas to those found in a similar study of conversion hysteria (leg paralysis)[113]. Though not conclusive, there is some indication that conversion disorder patients are more responsive to hypnotic suggestions[114] and research has shown hypnosis to be an effective treatment for various motor-type conversion disorders[115].

With integration of brain mapping techniques, hypnosis is a tool that can readily assist in characterizing discrete cognitive components in neurophysiological terms. Two qualifiers must be made, however: first, identifying brain areas associated with certain tasks or mental phenomena (such as visual hallucinations) does not disqualify that particular brain area from active involvement in other (non-hallucination) tasks; and second, isolating individual components associated with a given task does not provide a complete model of the neurophysiological processes involved with that task—identified brain areas are almost certainly part of a more distributed network of activation. The next step will be to identify the temporal relationship of activation in these distributed components.

## HYPNOSIS AS A DIAGNOSTIC TOOL

Considerable controversy surrounds provocation methods as a tool for differentiating epileptic and non-epileptic seizures. Non-epileptic seizures are reported in 10–23% of patients referred to epilepsy centers. While long-term video-EEG monitoring can commonly be used to detect distinguishing EEG changes accompanying clinical seizures, the expense, duration and accessibility of such techniques often makes it unfeasible. A number of physicians have used suggestive techniques such as an injection of saline or a placebo 'patch' to precipitate an attack. However, the necessary use of deception in such techniques presents certain ethical (and perhaps legal) dilemmas in terms of informed consent[116,117]. In light of this, it has been suggested that hypnotically provoked pseudoseizures can be elicited without the need for deception, and preliminary reports

have shown it to be an effective technique[118–120]. Regardless of the provocation method used, the induction of a psychogenic seizure does not rule out the possibility of epileptic seizures. Research has shown that between 10–20% of psychogenic seizure patients also have epileptic seizures. However, identification of psychogenic seizures can create improved outlook in patients, and psychotherapeutic interventions (including hypnosis[121]) have been shown to be effective in the reduction or elimination of seizures in such patients.[122]

## THE PROFESSIONAL PRACTICE OF HYPNOSIS

Anyone who can read a script with some degree of expression can learn how to hypnotize someone; as previously discussed, hypnosis is really a manifestation of an individual's hypnotic ability. There are countless certification programs available in the USA, Britain and worldwide. Certification can be obtained from weekend courses, correspondence courses and even through $100.00 web-based training. However, handing someone a wrench (even a 'certified' wrench) does not automatically make them a good mechanic. The most important factor in the clinical application of hypnosis is that the practitioner be qualified to treat the presented problem *without* the use of hypnosis. Hypnosis should never be viewed as a panacea. It is simply one of many tools that may be used by a qualified psychotherapist, dentist, nurse, or physician, when appropriate. Thus, probably the most important credential is state licensure in the practitioner's given profession.

Although it is not difficult to learn how to hypnotize someone, using hypnosis appropriately and effectively is a developed skill. Only with sufficient training in hypnosis will a practitioner be in the best position to decide whether hypnosis is indicated and, if it is, how it might be incorporated into the individual's treatment. In the USA, the Society for Clinical and Experimental Hypnosis (SCEH) and the American Society for Clinical Hypnosis (ASCH) offer specialized training in hypnosis to professionals with appropriate credentials, and both societies offer referral services for those seeking qualified practitioners. The current contact information for these societies, along with the British Society of Experimental and Clinical Hypnosis (BSECH), the British Society of Medical and Dental Hypnosis (BSMDH) and the International Society of Hypnosis (ISH), can be found in the Appendix.

## CONCLUSION

Hypnosis has a long, and at times colorful, history. In their investigation of Mesmer, the Royal Commission set the bar appropriately high. If we are to argue that hypnosis works, then we must demonstrate this with replicable evidence that can be explained in relation to current understandings of medical and cognitive science. There is now strong empirical support, including brain activation studies, for the use of hypnosis in pain management. Additionally, preliminary findings suggest that it is a 'possibly efficacious' treatment for a number of other conditions, including asthma and dermatological disorders, and that it may also enhance the effectiveness of certain types of psychotherapy. The integration of findings from research and clinical practice provides a

rich foundation for future investigations, both in the examination of the phenomenon itself and in the application of hypnosis as a research and diagnostic tool.

## APPENDIX

### Contact information for professional societies in hypnosis

Society for Clinical and Experimental Hypnosis
221 Rivermoor Street
Boston, MA 02132
USA
Tel: (617) 469–1981
Fax: (617) 469–1889
E-mail: sceh@mspp.edu
Web: http://ijceh.educ.wsu.edu
Journal: *The International Journal of Clinical and Experimental Hypnosis*

American Society of Clinical Hypnosis
140 N. Bloomingdale Road
Bloomingdale, IL 60108–1017
USA
Tel: (630) 980–4740
Fax: (630)351–8490
E-mail: info@asch.net
Web: http://www.asch.net
Journal: *The American Journal of Clinical Hypnosis*

British Society of Experimental and Clinical Hypnosis
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E-mail: honsec@bsech.com
Web: http://www.bsech.com
Journal: *Contemporary Hypnosis*

British Society of Medical and Dental Hypnosis
National Office, 28 Dale Park Gardens
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E-mail: ish-central.office@medicine.unimelb.edu.au
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# 11
# Religious involvement, spirituality and medicine: subject review and implications for clinical practice

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Adapted, with permission, from Mueller PS, Plevak DJ, Rummans TA. Religious involvement, spirituality, and medicine: implications for clinical practice. *Mayo Clin Proc* 2001; 76:1225–35


*Complementary Therapies in Neurology: An Evidence-Based Approach*
Edited by Barry S.Oken
ISBN 1-84214-200-3 

## INTRODUCTION

When people consult clinicians to determine the cause and treatment of an illness, they may also seek answers to existential questions that medical science cannot answer (e.g. 'Why is this illness happening to me?')[1]. Many patients rely on a religious or spiritual framework and call on religious or spiritual care providers to help answer these questions. Indeed, throughout history, religion and spirituality and the practice of medicine have been intertwined. As a result, many religions embrace caring for the sick as a primary mission, and many of the world's leading medical institutions have religious and spiritual roots.

The word 'religion' is from the Latin *religare*, which means 'to bind together'[2]. A religion organizes the collective spiritual experiences of a group of people into a system of beliefs and practices. 'Religious involvement' or 'religiosity' refers to the degree of participation in or adherence to the beliefs and practices of an organized religion. 'Spirituality' is from the Latin *spiritualitas*, which means 'breath'[2]. It is a broader concept than religion and is primarily a dynamic, personal and experiential process. Features of spirituality include quest for meaning and purpose, transcendence, connectedness (e.g. with others, nature, or the divine) and values (e.g. love, compassion and justice)[3]. Even though some people who regard themselves as spiritual do not endorse a formal religion, religious involvement and spirituality are overlapping concepts[4]. Experientially, both may involve a search for meaning and purpose, transcendence, connectedness and values. In this light, religious involvement is similar to spirituality. Spirituality may also have communal or group expression; when this

expression is formalized, spirituality is more like an organized religion[5]. Because of this overlap, religious involvement and spirituality are considered together in this chapter.

Religion and spirituality are among the most important cultural factors that give structure and meaning to human values, behaviors and experiences[6]. In fact, most people report having a spiritual life. Surveys of the general population[7] and of patients[8,9] have consistently found that more than 90% of people believe in a Higher Being. One survey[8] found that 94% of patients regard their spiritual health and their physical health as equally important. Most patients want their spiritual needs met and would welcome an inquiry regarding their religious and spiritual needs[8,10,11]. Finally, a survey of family physicians found that 96% believe spiritual wellbeing is an important factor in health[12]. Despite these findings, the spiritual needs of patients are often ignored or not satisfied[8,9,13] (Mayo Patient Expectations Survey, unpublished data, 1994). Nevertheless, clinician interest in patient spirituality has increased because of a growing number of studies that have shown an association between increased religious involvement and spirituality and better health outcomes[14].

This chapter reviews the results of published studies, meta-analyses, systematic reviews and subject reviews that have examined the association between religious involvement, patient spirituality and spiritual interventions (e.g. pastoral care) and physical health, mental health, health-related quality of life (HRQOL) and other outcomes. The studies selected used validated measures of religious involvement (e.g. attendance at religious services) and spirituality (e.g. scales of spiritual well-being) and statistical testing for significance. Finally, suggestions on how clinicians might ethically assess and support the spiritual needs of patients are provided.

Notably, intercessory prayer studies are not reviewed in this chapter. These studies do not examine the effects of patients' religious involvement and spirituality on their own health outcomes. Instead, intercessory prayer studies examine the effects of prayers of others (i.e. intercessors) on patient health outcomes. Furthermore, intercessory prayer studies have significant methodological flaws, making their relevance to clinicians unclear[15,16].

## USE OF RELIGIOUS AND SPIRITUAL VARIABLES IN MEDICAL RESEARCH

Religious and spiritual variables are not widely used in medical research. For example, a review[17] of 2348 studies published in four major psychiatry journals between 1978 and 1982 revealed that only 59 (2.5%) involved a religious or spiritual variable. A later review[18] of the same journals for 1991–95 revealed that only 1.2% of studies used such a variable. Similar reviews have shown that only 3.5% of family practice studies[19], 1.1% of internal medicine studies[20], 11.8% of adolescent health studies[21], 10% of nursing mental health studies[22] and 3.6% of gerontology studies[23] used religious or spiritual variables. Neglect of religious and spiritual variables in medical research may be attributable, in part, to the reliance on the biomedical model in which physical evidence is paramount. While the biomedical model is excellent for describing certain disease mechanisms (e.g. viral illnesses), it is reductionistic and has difficulty accounting for psychological, sociological and spiritual factors that influence most, if not all, illnesses[24].

Of the studies that have considered the effects of religious or spiritual factors on health, most have used measures of religious involvement (e.g. frequency of attendance at religious services and scales of religiosity), not measures of spirituality. The main reason for this practice is the greater consensus on how to define and measure religious involvement as opposed to spirituality.

## RELIGIOUS INVOLVEMENT, SPIRITUALITY AND PHYSICAL HEALTH

A majority of the nearly 350 studies of physical health that used religious and spiritual variables have found that religious involvement and spirituality are associated with better physical health outcomes[25].

### Mortality

During the past three decades, at least 18 prospective studies have shown that religiously involved persons live longer[26–43]. The populations examined in these studies included not only entire communities but also specific groups. The religious and spiritual variables used in these studies included membership in a religious congregation[29,31,34], attendance at religious Services[26–28,30,32,33,35,36,38–42], living within a religious community[37] and self-reported religiosity[43]. One study[44] of hospitalized veterans, however, found no relationship between religious involvement, religious coping and mortality. In addition, a 2-year longitudinal cohort study[45] of nearly 600 patients aged 55 years or older found that religious struggle with illness (e.g. questioning God's presence or love) was associated with increased risk of death.

Recent prospective studies have carefully controlled for potential confounding variables[46]. A 28-year study[38] of 5286 adults (aged 21–65 years) found that frequent (once per week or more) attenders of religious services were 23% less likely than non-attenders to die during the follow-up period (relative hazard 0.77; 95% confidence interval (CI) 0.64–0.93) adjusted for age, sex, ethnicity, education, baseline health status, body mass index, health practices and social connections. Notably, this study also found that mobilityimpaired persons were *more likely* to be frequent attenders than non-attenders. A 5-year study[39] examined the same relationship in 1931 adults (aged 55 years or older). Frequent attenders were 24% less likely to die than nonattenders during the follow-up period (relative hazard 0.76, 95% CI 0.62–0.94) adjusted for age, sex, marital status, income, education, employment status, ethnicity, baseline health status, physical functioning, health habits (e.g. exercise, smoking), social functioning and support and mental health status. A 6-year study[42] examined the same relationship in 3968 adults (aged 65 years or older). Frequent attenders were 28% less likely than infrequent (less than once per week) to die during the follow-up period (relative hazard 0.72, 95% CI 0.64–0.81) adjusted for demographic factors, health conditions, social connections and health practices. Finally, a 9-year study[41] of a nationally representative sample of 22080 American adults (aged 20 years or older) found the risk of death for non-attenders to be 1.87 times the risk of death for frequent attenders ($p<0.01$) after controlling for numerous demographic, baseline health, behavioral, social and economic variables.

A recent meta-analysis[47] of 42 studies of nearly 126000 persons found that highly religious persons had a 29% higher odds of survival compared with less religious persons (odds ratio (OR) 1.29, 95% CI 1.20–1.39). The authors could not attribute the association to confounding variables or to publication bias.

### Cardiovascular disease

Studies have found that religious involvement is associated with less cardiovascular disease. A case-control study[48] found that secular Jewish persons had significantly higher odds of first myocardial infarction compared with Orthodox Jewish patients (men: OR 4.2, 95% CI 2.6–6.6; women: OR 7.3, 95% CI 2.3–23.0) adjusted for age, ethnicity, education, smoking, physical activity and body mass index. A 23-year prospective study[49] of 10059 male Israeli civil servants and municipal employees found that Orthodox Jewish men had a 20% decreased risk of fatal coronary heart disease (CHD) compared with non-religious men adjusted for age, blood pressure, lipids, smoking, diabetes, body mass index and baseline CHD. A prospective study[50] of 232 people (aged 55 years or older) undergoing elective heart surgery found that lack of participation in social groups and lack of strength or comfort from religion were the most consistent predictors of death adjusted for age, previous cardiac surgery and preoperative functional status. Finally, of 16 studies examined in a recent review[51], 12 found that religious involvement was associated with less cardiovascular disease or cardiovascular mortality.

### Hypertension

Studies have found that religious involvement is associated with lower blood pressure and less hypertension. Koenig and colleagues[52] examined the relationship between religious activities and blood pressure in a sample of 3963 community-dwelling adults (aged 65 years or older) using data from three time periods. Adjusted for age, ethnicity, sex, education, functional status, body mass index and previous blood pressure, frequent (once per week or more) attenders of religious services had consistently lower systolic and diastolic blood pressures compared with infrequent attenders. Furthermore, frequent attenders who engaged in private religious activities (e.g. prayer) were 40% less likely to have diastolic hypertension (>90mmHg) compared with infrequent attenders or those who did not engage in private religious activities (OR 0.60, 95% CI 0.48–0.75). Religiously involved persons were also more likely to be compliant with their medicines. However, this difference did not account for the observed differences in blood pressure.

Other studies[53,54] have found that, after adjusting for known risk factors for hypertension, self-rated importance of religion, intrinsic religiosity and religious coping were associated with reduced blood pressure and hypertension. Finally, of 16 studies examined in a recent review[51], 14 found that religious involvement was associated with lower blood pressure. The same review also examined 13 clinical trials of the effects of religious or spiritual practices (e.g. meditation) on blood pressure. Of these, nine found that these practices significantly reduced blood pressure.

### Other studies of physical health

Studies have shown that religious involvement is associated with health-promoting behaviors such as more exercise[55–57], proper nutrition[55,56], more seat belt use[55], smoking cessation[57] and greater use of preventive services[27]. In addition, religious involvement predicted greater functioning among disabled persons[58]. Finally, religious involvement was associated with fewer hospitalizations and shorter hospital stays[59]. Only a few inconclusive studies have been carried out on the relationship between religious involvement and spirituality, and cancer risk and mortality[51].

## RELIGIOUS INVOLVEMENT AND SPIRITUALITY IN TERMINALLY ILL PATIENTS

The World Health Organization's definition of palliative medicine emphasizes the psychosocial and spiritual aspects of care[60]. End-oflife care addresses not only physical symptoms but also psychosocial and spiritual concerns. Terminally ill patients derive strength and hope from spiritual and religious beliefs[61,62]. Indeed, terminally ill adults report significantly greater religiousness[63] and depth of spiritual perspective[64] compared with healthy adults. Greater depth of spiritual perspective is associated with greater sense of well-being[64]. Studies[61,65] also suggest that religiously involved persons at the end of life are more accepting of death, unrelated to belief in an afterlife. Finally, intrinsic religiosity[66,67] and religious involvement[68] are associated with less death anxiety.

## RELIGIOUS INVOLVEMENT, SPIRITUALITY AND MENTAL HEALTH

A majority of the nearly 850 studies of mental health that have used religious and spiritual variables have found that religious involvement and spirituality are associated with better mental health outcomes[25].

### Depression

Depression is a common illness; 6–10% of the population experience significant depression during their lifetime[69]. Recent longitudinal studies have examined the relationship between religious involvement and spirituality and depression. One study[70] examined the effects of self-reported religious salience on the incidence and course of depression in a community-based sample of 177 persons (aged 55–89 years) in 1 year. Religious salience not only was associated with less risk of depression but also was strongly associated with recovery from depression among those who were depressed at the start of the study (especially those in poor physical health). Another study[71] examined the association between intrinsic religiosity and remission of depression among 94 depressed, medically ill men (aged 60 years or older) in 1 year. After adjustment for 27

potential confounding variables, intrinsic religiosity was significantly associated with a greater likelihood of remission and a more rapid remission from depression.

In a study[72] of the treatment of depressed religious persons, standard cognitive-behavioral therapy (CBT) was compared with a combination of standard CBT with religious content, and with pastoral care alone. The patients who received CBT with religious content or pastoral care alone had significantly less post-treatment depression compared with those who received only standard CBT. In a similar study[73], investigators randomly assigned religious Muslim patients with depression to standard therapy (medications and supportive psychotherapy) or to standard therapy with religious psychotherapy. Those receiving religious psychotherapy experienced a significantly more rapid recovery than those receiving standard therapy alone.

A recent review[74] examined the relationship between religious involvement and depression. Of 29 studies that examined this relationship, 24 found that religiously involved persons had fewer depressive symptoms and less depression, whereas the remaining five studies found no association.

### Anxiety

Religious involvement has been shown to be associated with less anxiety. One study[75] examined the relationships between multiple religious variables (e.g. attendance at religious services, self-rated importance of religion and private religious activities) and recent and lifetime anxiety disorders among nearly 3000 adults. Controlled for sex, chronic illnesses, negative life events and socioeconomic status, religious involvement was associated with decreased recent and lifetime anxiety among the youngest patients (aged 18–39 years), but not among the oldest (aged 60–79 years). Another study[76] examined the relationship between spiritual well-being and anxiety in 114 adults with newly diagnosed cancer. Patients with high levels of spiritual well-being had lower levels of anxiety regardless of sex, age, marital status, diagnosis, group participation, or time since diagnosis.

Notably, two randomized clinical trials[73,77] involving religious Muslim patients with anxiety disorder compared standard therapy (medications and supportive psychotherapy) with standard therapy and religious psychotherapy. Those who received religious psychotherapy experienced a significantly more rapid recovery than those receiving standard therapy alone.

A recent review[51] of nearly 70 cross-sec-tional and prospective studies found that religious involvement was associated with less anxiety or fear.

### Alcoholism, cigarette smoking and other forms of substance abuse

Religious persons are less likely to use or abuse alcohol and other drugs[7,55,56]. Areview[78] of 20 studies published before 1976 found that religious involvement was associated with less substance abuse whether the study was prospective or retrospective and whether the measure of religious involvement was defined as membership, active participation, religious upbringing, or self-reported religious salience. More recent reviews[51,79] have found similar results.

Longitudinal studies of religious involvement and substance abuse have been performed. One prospective study[80] of 1014 male medical students found that religiously involved students were much less likely to abuse alcohol than their non-religious colleagues during a 20-year follow-up period. One randomized trial[81] compared spiritually based 12-step facilitation (TSF) therapy with CBT and motivational enhancement therapy for alcoholism. TSF was designed to engage patients in Alcoholics Anonymous (AA) and to assist patients through the first steps of the AA spiritual program. Compared with the other groups, TSF patients were significantly more likely to achieve complete abstinence.

A number of cross-sectional studies have found an inverse relationship between religious involvement and cigarette smoking[51]. Notably, a recent 3-year prospective cohort study[82] of 4569 adults aged 20–32 years had similar results. In that study, the odds of current smoking were higher among infrequent (less than once a month) attenders of religious services compared with frequent (at least once a month) attenders (OR 1.7, 95% CI 1.5–2.0). In addition, non-smokers who were infrequent attenders were more likely to start smoking compared with frequent attenders (OR 1.9, 95% CI 1.3–2.7). Finally, religious involvement was associated with greater likelihood of smoking cessation[57].

A review by Miller[83] concluded that there was strong evidence that religious or spiritual involvement was associated with decreased risk of substance abuse, that persons with addictions were more likely to report a lack of religious affiliation and involvement and that spiritually focused interventions (i.e. focused on meaning and purpose, not necessarily on specific religious beliefs) and practices (e.g. prayer) may facilitate recovery.

### Suicide

The inverse relationship between religious involvement and suicide was first reported in 1897[84]. Since then, a number of studies have confirmed this inverse relationship. Self-reported religiosity[85] and attendance at religious services[85–87] have been shown to be inversely associated with suicidal ideation. Two large ecological studies[88,89] of Western countries and a cross-sectional study[90] of a representative sample of Americans found inverse relationships between religious involvement and acceptance of suicide. One study[91] found that religious detachment was associated with increased suicide risk among Canadian youth. Several large ecological studies have found that belief in God[92], attendance at religious services[93], self-reported religiosity[89,93] and religious upbringing[93] were inversely related to national suicide rates. Finally, several prospective studies[28,37] have found that the risk of completed suicide among religiously involved persons was less than the risk among non-religiously involved individuals. Despite these findings, most scales currently used by researchers and clinicians to assess suicide risk do not assess patient religiosity or spirituality[94].

## RELIGIOUS INVOLVEMENT, SPIRITUALITY AND COPING

Needless to say, surviving a natural disaster or crime, caring for a sick relative or friend, and experiencing the death of a loved one can be distressing experiences. Religious

involvement, however, may mitigate the adverse effects of these experiences[51]. In fact, religious involvement is associated with quicker resolution of grief. A recent prospective[95] cohort study included 135 relatives and close friends of patients with terminal illness who were followed for up to 14 months after their loved one's death. Those who professed strong religious and spiritual beliefs experienced quicker and more complete resolution of their grief compared to those without such beliefs.

Illnesses can also be a distressing experience. Illnesses interrupt routines, drain finances, separate families, create situations of dependency and may lead to existential and spiritual concerns[60]. Not only do many people rely on their religious beliefs and spirituality to cope with illness, but these people may also cope with illness more effectively than persons without such beliefs[7]. Religious and spiritual coping is common among persons with asthma[96], human immunodeficiency virus (HIV) disease[97], chronic pain[98,99], coronary,[98,99] artery disease[100,101], end-stage renal disease[100,102], multiple sclerosis[100], burns[103,] hip fracture[104], and cancer[105–113]. Religious and spiritual coping are also common among nursing-home residents[114] and the elderly[115,116]. In a study of 122 hospitalized adults with moderate to high levels of pain, prayer was second only to oral pain medications (62 vs. 67%) as the most common self-reported means of controlling pain[98].

Religious and spiritual coping may have important prognostic implications. Cross-sectional and longitudinal studies have shown that religious and spiritual coping were associated with less depression during illness[104,116–119]. One study[117] examined the relationship between religious coping and depression among 850 men (older than 65 years) who had no history of mental illness and were hospitalized for a medical illness. After adjusting for sociodemographic and baseline health variables, depressive symptoms were inversely related to religious coping. In addition, religious coping was the only baseline variable that predicted less depression 6 months later.

Religious and spiritual coping have also been shown to lessen the negative impact physical illness has on functional status[7,117]. The greater the religious and spiritual coping, the greater the level of physical illness needed to produce a given level of disability. Finally, religious and spiritual coping has been shown to buffer the noxious effects of stressful life events (e.g. death of spouse, divorce) among the elderly[120].

## RELIGIOUS INVOLVEMENT, SPIRITUALITY AND HEALTH-RELATED QUALITY OF LIFE

The terms 'quality of life' and, more specifically, 'health-related quality of life' refer to the distinct physical, psychological, social and spiritual domains of health that are influenced by a person's experiences, beliefs, expectations and perceptions[121]. Studies have shown that religious involvement and spiritual well-being are associated with high levels of HRQOL in persons with cancer[68,122–125], HIV disease[122,125], heart disease[68], limb amputation[123] and spinal cord injury[123]. This direct relationship between spirituality and HRQOL persists despite declines in physical functioning[122,125]. One study[125] of 1620 persons with cancer and HIV disease found that spiritual well-being predicted higher HRQOL, independently of physical, emotional and social well-being.

## NEGATIVE EFFECTS OF RELIGIOUS INVOLVEMENT AND SPIRITUALITY

Few systematic population-based studies have shown that religious involvement and spirituality are associated with negative health outcomes. However, like any factor that may impact health (e.g. lifestyle choices), religious involvement and spirituality may adversely affect an individual. For example, religious beliefs may adversely affect a person's physical health by encouraging avoidance or discontinuance of traditional treatments, failure to seek timely medical care, avoidance of effective preventive health measures (e.g. childhood immunizations and prenatal care) and religious abuse (e.g. allowing for physical abuse of children). Religious involvement and spirituality may also adversely affect an individual's mental health. For example, mentally ill religious persons may avoid psychiatric care. Religiously involved persons may have unrealistically high expectations for themselves, leading to isolation, stress and anxiety, or they may alienate themselves from others who do not share their beliefs. Finally, it is well known that unhealthy belief systems (e.g. cults) can adversely affect health[51].

Notably, Sigmund Freud and Albert Ellis regarded religious involvement as suggestive of psychopathology[126]. This opinion, however, was not derived from research. In fact, investigators have tested the hypothesis that religious involvement is associated with mental illness. A meta-analysis[127] of 24 such studies found no association between religious involvement and psychopathology.

**Table 1** Religious involvement, spirituality and health outcomes. Reproduced with permission from Mueller PS, Plevak DJ, Rummans TA. Religious involvement, spirituality, and medicine: implications for clinical practice. *Mayo Clin Proc* 2001; 76:1225–35

| |
|---|
| *What the research tells us* |
| Most persons have a spiritual life |
| Most patients want their spiritual needs assessed and addressed |
| Most studies have found a direct relationship between religious involvement and spirituality and better health outcomes |
| Supporting a patient's spirituality may enhance coping and recovery from illness |
| *What the research does not tell us* |
| Religious people don't get sick |
| Illness is due to lack of religious faith |
| Spirituality is the most important health factor |
| Doctors should prescribe religious activities |
| Other factors explain the association between religious involvement and spirituality and better health outcomes |

## WHAT CONCLUSIONS CAN BE DRAWN FROM THE RESEARCH?

According to Levin[128], to verify a causal relationship between a variable (e.g. religious involvement) and a health outcome (e.g. mortality), three questions must be answered. Is there an association? If so, is the relationship valid? If so, is it causal? Regarding the first question, a majority of nearly 1200 studies have found a direct relationship between religious involvement and spirituality and better health outcomes[25].

The association between religious involvement and spirituality and better health outcomes seems valid. This association has been found regardless of study design (e.g. prospective, retrospective) and the population studied. In addition, religious and spiritual variables were not the primary or the only ones used in most studies. These study design features limit bias. Furthermore, recent well-designed studies have shown a direct relationship between religious involvement and spirituality and better health outcomes even after adjusting for potential confounding variables[46].

Whether religious involvement and spirituality cause better health outcomes is more difficult to determine. Levin[128] describes nine features of a causal epidemiological association: strength, consistency, specificity, temporality, biological gradient, plausibility, coherence, experiment and analogy. For some of these features (strength, consistency, temporality, plausibility, analogy), the published studies support causality, whereas for the others, there is insufficient evidence.

Even though the association between religious involvement and spirituality and better health outcomes appears valid, clinicians should be careful not to draw erroneous conclusions from the research findings (Table 1[129]). For example, the research does not tell us that religious people do not get sick or that illness is caused by lack of religious faith.

## POSSIBLE BENEFICIAL MEDIATORS OF RELIGIOUS INVOLVEMENT AND SPIRITUALITY

Like other factors that promote health (e.g. exercise), religious involvement and spirituality probably enhance resistance to disease through the interaction of multiple beneficial mediators. Members of a religious group may have a shared genetic ancestry that promotes health[130]. Developmental factors may also mediate the effects of religious involvement on health. For example, children who are born into religiously involved families may not only learn healthy behaviors but also view their religious and spiritual relationships (including the relationship with God) as sources of hope, comfort and support[51]. Indeed, religiously involved persons often have strong social support systems, the health benefits of which are well known,[57,130–132]. Further more, as discussed above, religiously involved persons seem more capable than uninvolved persons of coping with stressful life events. These factors lead to better mental health outcomes.

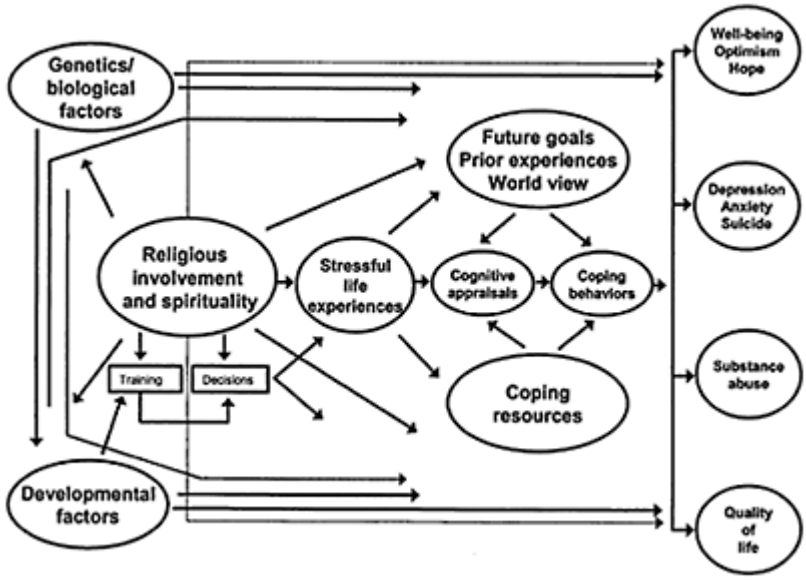


**Figure 1** Theoretical model of the effects of religious involvement and spirituality on mental health. Reproduced with permission from Koenig HG, McCullough ME, Larson DB. *Handbook of Religion and Health.* New York: Oxford University Press, 2001

In turn, good mental health, strong social support and salutary health behaviors lead to improved physical health. As reviewed previously, religiously involved persons are more likely to embrace health-promoting behaviors, such as eating a proper diet, to eschew risky behaviors such as smoking, to seek preventive services and to adhere with prescribed treatments.

In addition, religious and spiritual practices (e.g. meditation, prayer and worship) can engender positive emotions such as hope, love, contentment and forgiveness, and limit negative emotions such as hostility. Positive emotions, in turn, can limit the activation of the sympathetic branch of the autonomic nervous system and the hypothalamic-pituitary-adrenal axis (and decreased release of stress hormones such as norepinephrine (noradrenaline) and cortisol). This response has not only psychological effects (e.g. less anxiety), but also physiological effects (e.g. decreased blood pressure, heart rate and oxygen consumption) that may lead to better health[131–133]. In fact, compared with uninvolved persons, religiously involved persons have enhanced immune function[51].

Finally, the placebo effect is a commonly observed phenomenon in medical research and practice. Religiously involved persons may have greater optimism and expectation for better health outcomes and, hence, benefit from the placebo effect[130] .

Not all the mechanisms by which religious involvement and spirituality affect health are understood, and more studies are needed for better definition of them. These mechanisms undoubtedly involve complex interactions of psychosocial-behavioral and biological processes[51]. Nevertheless, theoretical models of the effects of religious involvement and spirituality on mental and physical health that account for these interactions have been developed (Figures 1 and 2). Of note, this chapter does not attempt to account for the religious beliefs (e.g. regarding the supernatural) individuals may have regarding the effects of religious involvement and spirituality on health.

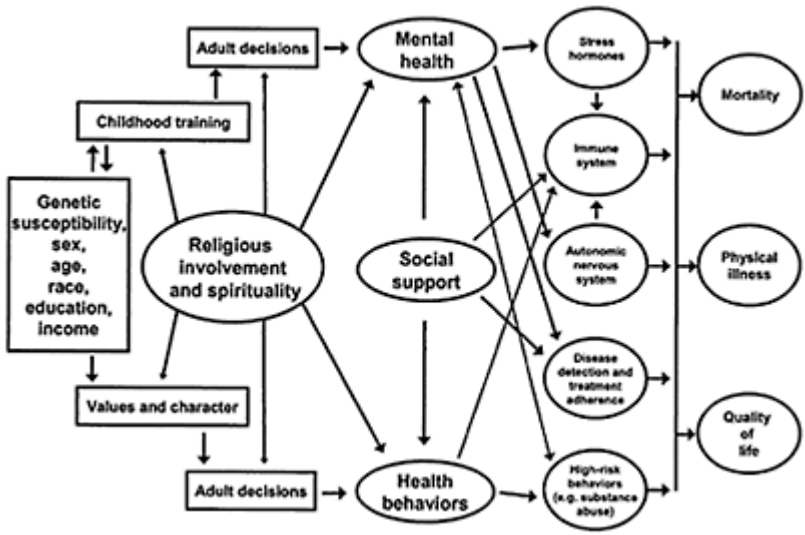


**Figure 2** Theoretical model of the effects of religious involvement and spirituality on physical health. Modified with permission from Koenig HG, McCullough ME, Larson DB. *Handbook of Religion and Health.* New York: Oxford University Press, 2001

## CLINICAL IMPLICATIONS OF PATIENTS' RELIGIOUS INVOLVEMENT AND SPIRITUALITY

### Practical aspects

The results of the surveys and the studies reviewed above suggest that patient care may be enhanced by acknowledging and supporting patient spirituality. Indeed, William Osler[134] called faith 'an unfailing stream of energy', whereas William J.Mayo[135] said that 'there is a spiritual as well as a material quality in the care of sick people, and too great efficiency in material details may hamper progress'. Today, the US Joint Commission on the Accreditation of Healthcare Organizations[83] recommends and requires the routine assessment of patients' spiritual needs, and the American Psychiatric Association[136] recommends that clinicians inquire about the religious and spiritual orientation of patients 'so that they may properly attend to them in the course of treatment'.

Nevertheless, most clinicians do not initiate discussions of spirituality with patients[137]. However, there are compelling reasons for clinicians to inquire about their patients' spiritual needs. First, patients regard their spiritual health and physical health as equally important[8]. Second, research suggests that a patient's spirituality improves coping and enhances quality of life during illness; it can be a source of identity, meaning, purpose, hope, reassurance, and transcendence, and it can mitigate the uncertainties of illness[5,138]. Third, acknowledging and addressing a patient's spirituality may enhance cultural sensitivity and enrich the clinician- patient relationship[5,138]. Fourth, many patients base their health-care decisions on their spiritual or religious beliefs[139]. Finally, patients suffering from religious, spiritual, and existential concerns may not inform their clinicians about them[139]. Because the goals of medicine are to cure disease when possible and to relieve suffering always[140], including spirituality in clinical practice should be within the purview of the physician. Supporting a patient's spirituality recognizes the patient as a whole person and should be viewed in the same light as addressing other psychosocial factors (e.g. family discord) that influence the delivery of care and the outcomes of illness.

Nevertheless, a number of barriers prevent support of patient spirituality. First, many clinicians practice in the biomedical model in which spiritual matters seem less relevant. Second, fewer physicians than patients describe themselves as religious or maintain spiritual orientations[9,141,142]. Hence, the importance of spiritual matters to patients may be underestimated or unrecognized. Third, the effect of religious involvement and spirituality on health outcomes is taught infrequently in medical training[141]. Fourth, some patients (e.g. children) may have complex or daunting spiritual needs that may discourage clinician involvement[143]. Finally, the spiritual concerns of patients may not be addressed because of time constraints, lack of confidence in the effectiveness of spiritual care and role uncertainty (e.g. with chaplains)[144].

## Ethical issues

Ethical issues are raised when one includes patient spirituality in clinical practice. The principle of non-maleficence ('do no harm') suggests that clinicians should avoid proselytizing to patients. Many patients derive hope and strength from their personal religious beliefs, and proselytizing to them may cause unnecessary harm. In addition, the results of the studies reviewed above do not justify a clinician's prescription for patients to engage in religious activities[145]. The ethical clinician would not make such recommendations, just as she or he would not recommend that patients marry or have children, even though these activities are associated with health benefits[145]. Finally, religious and spiritual practices should not replace effective allopathic treatments[25].

The beneficent clinician acknowledges and supports a patient's spirituality. Some authors, however, claim that the religious and spiritual concerns of patients are private and that clinicians should not inquire about them[145]. However, a similar case could be made regarding inquiries about patient sexuality, substance abuse and other sensitive matters. These matters, formerly shunned by clinicians, are now discussed openly because of their potential effect on health. The clinician's duty is not to judge a patient's private attitudes and behaviors but to understand their clinical importance[46,146]. Hence, clinicians should inquire about and support a patient's spiritual beliefs and needs, especially during severe and terminal illnesses, when they are most likely to affect clinical decisions. Indeed, lack of appropriate spiritual care may constitute a form of negligence.[138]

Some authors suggest that clinicians ignore patient spirituality because they may not have the knowledge or skills to engage religiously diverse patients in meaningful discussions about their spiritual needs without offending them[145]. Autonomy, however, requires that clinicians respect the decisions of competent patients, which are often based on religious and spiritual beliefs. Furthermore, unrelated to medical decisions, patients often spontaneously raise spiritual issues and concerns with their clinicians. Hence, it is difficult for clinicians to ignore or avoid patient spirituality.

## Taking a spiritual history and discussing and responding to spiritual concerns

The medical interview involves more than information gathering. It also involves relationship building and patient education[147]. Indeed, interviews that are clinician controlled and narrowly biomedical are associated with reduced patient and clinician satisfaction, whereas interviews that are open-ended and patient controlled and incorporate psychosocial factors are associated with greater satisfaction[148]. Hence, inquiring about spirituality may strengthen the clinician-patient relationship[5,138].

Discerning the spiritual needs of patients can be straightforward by taking a spiritual history. Similar to the social history, the spiritual history informs the clinician of the importance of spiritual matters in the life of the patient and how the patient's spirituality may be used as a source of strength and coping. For terminally ill patients, the spiritual history is regarded as a crucial component of palliative medicine[149–151].

Several formats for taking a spiritual history have been suggested[25,141,152]. One easy-to-use

**Table 2** The FICA spiritual history. Reproduced from Puchalski CM. Spirituality. In Berger AM, Portenoy RK, Weissman DE, eds. *Principles and Practice of Palliative Care and Supportive Oncology*, 2nd edn. Philadelphia: Lippincott Williams & Wilkins, 2002:799–812[153]. By permission of the publisher and Christina M. Puchalski

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|---|
| **Faith and belief**<br>'Do you consider yourself spiritual or religious?' or 'Do you have spiritual beliefs that help you cope with stress?' If the patient responds 'no', the physician might ask, 'What gives your life meaning?' Sometimes patients respond with answers such as family, career, or nature. |
| **Importance**<br>'What importance does your faith or belief have in your life? Have your beliefs influenced how you take care of yourself in this illness? What role do your beliefs play in regaining your health?' |
| **Community**<br>'Are you a part of a spiritual or religious community? Is this of support to you and how? Is there a group of people you really love or who are important to you?' Communities, such as churches, temples, mosques, or a group of like-minded friends, can serve as strong support systems for some patients. |
| **Address/action in care**<br>The physician and other health care providers can think about what needs to be done with the information the patient shared—referral to chaplain, other spiritual care provider, or other resource. |

and practical questionnaire[153] is shown in Table 2. Open-ended questions that can also help discern a patient's spiritual concerns and needs include 'What gives you hope and strength?'; 'To whom do you turn when you need support?'; 'What meaning does this illness have for you?'; and 'What are your expectations (fears) for the future?'[138,139,154]

A spiritual history is not necessary for every clinical encounter (e.g. patients with mild illnesses such as viral pharyngitis). Some patients, regardless of the severity of their illness, may not welcome in-depth discussion of spiritual matters. On the other hand, patients with life-threatening or terminal illnesses may be preoccupied with existential and spiritual concerns such as questioning of faith, lack of meaning and purpose and mystical and neardeath experiences[6,155]. The spiritual history can help uncover these concerns.

The spiritual history and open-ended questions such as those listed above may uncover important patient religious and spiritual concerns. When these concerns arise, clinicians should not abandon the patient but seek to acknowledge, understand and address the concerns. Improved understanding of concerns can be achieved by inviting the patient to share more information (e.g. 'Tell me more about that'). Clinicians should use phrases that normalize and legitimize the concerns (e.g. 'Many patients have similar concerns').

Phrases that convey empathy (e.g. 'I can see that you are troubled by this concern'; 'I imagine it has been frustrating not to know what will happen next') and respect (e.g. 'I admire your courage') should be used. Clinicians should also engender a spirit of partnership and support (e.g. 'We are in this together'; 'I will be here for you')[139,147] (Table 3).

When discussing religious and spiritual concerns with patients, clinicians should avoid a number of pitfalls[139]. Spiritual leads (e.g. the praying patient; patient asks 'Why is God punishing me?') should not be ignored. The discussion of spiritual concerns should not be rushed, and interruptions (e.g. pagers) should be avoided. Clinicians should not go beyond their expertise and role. In these circumstances, appropriate consultation (e.g. chaplain) should be obtained. Furthermore, they should avoid proselytizing and attempting to answer questions that cannot be answered. Finally, unhelpful phrases (e.g. 'It's God's will'; 'Nothing more can be done'; 'It could be worse') should be avoided (Table 4).

**Table 3** Phrases and questions that assist with eliciting the religious and spiritual concerns of patients. Adapted with permission from reference 139. Additional data from reference 147

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| *Use open-ended questions* |
| What gives you hope and strength? |
| What meaning does this illness have for you? |
| What are your expectations (fears) for the future? |
| How do you feel about…? |
| *Improve understanding of concerns by inviting the patient to share more information* |
| Tell me more about that. |
| What else concerns you? |
| *Normalize and legitimize the patient's concerns* |
| Many patients have similar concerns. |
| *Convey empathy and respect* |
| I can see that you are troubled (sad, perplexed, etc.) by this concern. |
| I imagine it has been frustrating not to know what will happen next. |
| I admire your courage. |
| *Engender a spirit of partnership and support* |
| We are in this together. |
| I will be here for you. |

## Sources of spiritual care

On its own, inquiring about religious and spiritual concerns can be a form of spiritual care. Allowing patients to voice their spiritual concerns and needs may be reassuring and comforting to them[156]. Informing patients of and mobilizing other sources of spiritual care may also be reassuring and limit the isolation experienced during illness[139]. Chaplains are an important source of spiritual care. Many medical centers have pastoral care departments staffed by chaplains who represent many religious faiths and

denominations. Chaplains are important sources for presence, support, counseling, sacramental needs and guidance regarding spiritual issues. Pastoral care departments also have access to community resources such as local congregations, spiritual care providers representing minority faiths, support groups and parish nurses. Other important sources of spiritual care include

**Table 4** Pitfalls to avoid when discussing religious and spiritual concerns with patients

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| *Ignoring spiritual leads*<br>The praying patient<br>The patient with religious jewelry, texts, etc<br>The patients who asks, 'Why is God punishing me?' |
| *Rushing the discussion* |
| *Responding to interruptions (e.g. pagers) Going beyond expertise and role*<br>In these circumstances, obtain appropriate consultation (e.g. chaplain) |
| *Proselytizing* |
| *Attempting to answer questions that cannot be answered* |
| *Using unhelpful phrases*<br>'It's God's will'<br>'Nothing more can be done'<br>'It could be worse' |

**Table 5** Sources of spiritual care. Reproduced with permission from Mueller PS, Plevak DJ, Rummans TA. Religious involvement, spirituality, and medicine: implications for clinical practice. *Mayo Clin Proc* 2001; 76:1225–35

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|---|
| Physician's and other health-care provider's acknowledgment and support of a patient's spiritual needs |
| Chaplains |
| Family and friends |
| Community resources (e.g. clergy, parish nurses, support groups) |
| Readily available religious texts and artifacts |
| Chapels |
| Quiet rooms, meditation rooms |

family and friends, readily available religious texts, artifacts, hospital chapels and special rooms devoted to prayer and meditation (Table 5).

## CONCLUSIONS

Most patients have a spiritual life and regard their spiritual health and physical health as equally important. Furthermore, people may have greater spiritual needs during illness. Surveys suggest, however, that these needs are not usually met.

A large and growing number of studies have shown a direct relationship between religious involvement and spirituality and positive health outcomes, including mortality, physical illnesses, mental illness, HRQOL, and coping with illness (including terminal illness). Studies also suggest that addressing the spiritual needs of patients may facilitate recovery from illness.

Although the relationship between religious involvement and spirituality and health outcomes seems valid, it is difficult to establish causality. While religiously involved persons embrace health-promoting behaviors, eschew risky behaviors and have strong support networks, these factors do not account for all of the salutary benefits of religious involvement and spirituality. Rather, these benefits are likely to be conveyed through complex psychosocial-behavioral and biological processes that are incompletely understood.

Discerning, acknowledging and supporting the spiritual needs of patients can be done in a straightforward, ethical and non-controversial manner and may relieve suffering and facilitate recovery from illness. The spiritual history and the open-ended questions reviewed above help the clinician discern the spiritual needs of patients. Furthermore, such inquiry is a form of spiritual care, in that it allows patients to voice their spiritual and existential doubts. In addition, many other sources of spiritual care, especially chaplains, are available to address the spiritual concerns and needs of patients. Addressing the spiritual concerns and needs of patients may be a valuable adjunct to standard medical care.

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# 12
# Placebo effect: clinical perspectives and potential mechanisms

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*Complementary Therapies in Neurology: An Evidence-Based Approach*
Edited by Barry S.Oken
ISBN 1-84214-200-3 

## INTRODUCTION

'Placebo' and 'placebo effect' are terms that have multiple meanings and connotations and have had a varied history over the past 50 years[1–3]. The terms may not beideal, because of negative associations, but the terms are in widespread use with several books on the topic[2,4,5]. There is an effect on subjective or biomarker outcomes in many clinical interactions, including clinical trials, owing to a substance or procedure for which we do not expect there to be a direct biological effect on the underlying primary pathophysiology. These indirect or non-specific effects of biologically inert substances or inactive procedures come under the general term *placebo effects.* It is likely that much improvement in patients following an encounter with a health-care provider is mediated via fairly indirect mechanisms and not at the specific underlying pathophysiology of the disease the patient may have. Some have suggested that much of the improvement patients experience following encounters with complementary health-care providers is related to the placebo effect, but the same could be said for patients seen by conventional medical providers[6]. The placebo issue is particularly problematic in complementary medicine, because of the frequent lack of patient blinding with some complementary therapy studies[7]. Although placebo effects contribute to variability in outcome data that are at least partially independent of known direct biological effects of the interventions, simply considering placebo as noise or confounding in clinical trials is not helpful in understanding the mechanisms.

The intervention that elicits the placebo effect is referred to as the placebo. The placebo can be any clinical intervention including words, gestures, pills, devices, and surgery[8]. The term 'sham' is sometimes used to describe a placebo intervention, such as in the context of surgery, but the use of the term is not ideal, because of its negative connotation. This chapter does not focus on the ethical issues related to the use of placebo clinically or in clinical trials which have been discussed elsewhere[9,10].

Expectancy is a major component of the placebo effect[11]. 'Expectancy' here is meant as a broad term and includes all processes and influences, ranging from classical

conditioning to culture, that may affect the brain's anticipation of a response. There are other indirect effects related to expectancy that impact health besides the placebo effect. These include the delay in mortality prior to an important event, 'voodoo death'[12–14], the impact of Chinese birth year sign on mortality related to diseases associated with the birth year sign among Chinese[15], the impact of pessimism, depressed affect and hopelessness on disease and function[16–18] and the nocebo effect[19,20]. The nocebo effect is presumably related to the placebo effect, but represents a negative outcome as opposed to the positive outcome of the placebo effect. Uncertainty in diagnosis and prognosis[21], and uncertainty in your country's soccer team's ability to win a penalty shootout[22] may impact health outcomes as well, possibly through some mechanism related to stress or anxiety. Since the biological mechanism of all these effects may be similar to the placebo effect, in terms of how expectancies impact health, some have suggested discussing the placebo effect in the more general framework of a *meaning response*[23,24]. This may be a more neutral term than placebo effect or expectancy. The meaning response perhaps can more easily incorporate sociocultural issues as well as the nocebo effect. 'Context effects' is another term that has been used similarly to describe the placebo effects[25].

## METHODOLOGICAL ISSUES CONFOUNDING PLACEBO EFFECT STUDIES

There are several methodological issues that have produced misinterpretations of studies relating to the placebo effect, even recent publications. These methodological concerns include natural history, the Hawthorne effect, regression to the mean, therapist and observer biases, direct treatment effects confounding the placebo arm of a study and other aspects of poor experimental design[26]. Natural history is simply what would have happened to a patient independently of any intervention (placebo or active treatment). In the most stringent definition it is also independent of being in a clinical trial. It is difficult to study placebo effects in diseases where the natural healing rate is high (e.g. ulcer disease) or where spontaneous fluctuations are common (e.g. multiple sclerosis). The natural history effect is important to take into account when studying the placebo effect. Unfortunately, it is rare in modern clinical trials to have untreated control groups. As a result, a recent systematic review of the placebo effect found only 114 clinical trials spanning several decades that had both a placebo treatment arm as well as a non-treatment arm in a clinical trial. Most of the studies were published prior to 1990, with 24 of them published prior to 1980[27]. The effect of placebo in this meta-analysis was seen only in continuous outcome measures and not in binomial outcome measures. Many of the papers discussed in this chapter compare different placebo arms, but do not compare a placebo group to a non-treatment group in the same study. Thus, natural history may be confused with placebo effect in these papers and contribute to uncertainty about the frequency and magnitude of the placebo effect.

There are some effects on outcome measures that result simply from being in a clinical trial, independent of any intervention, be it an active treatment or placebo. For example, subjects may change health habits simply from being in a study. This effect, related solely to a change in behavior secondary to simply being in a study and undergoing

assessments, is referred to as the Hawthorne effect[28]. The Hawthorne effect contributes to confusion about placebo effects.

Regression to the mean is the tendency of the second measurement of an outcome measure to be closer on average to the mean than the first measurement, performed at study onset. For example, one measures memory in a group of 100 healthy adults and takes the 20 adults with the poorest memory scores to be tested at a later time. Most of the 20 subjects who are retested will show improvement compared with their first score. Their improved scores will be closer to the mean than they originally were, because it was partially by chance that they had poor values at the time of the first assessment. This statistical effect can easily be confused with placebo effect in clinical studies[29].

Subject and clinician biases are problems throughout clinical science but are especially problematic in terms of studying the placebo effect. Subjects may have biases such as magnifying sick responses to be included in the study as well as rating themselves better than they are at the end so that they are considered good patients.

Subject biases may occur when the blinding is not ideal and subjects perceive they are receiving the active drug or other treatment. This is especially problematic in crossover trials, where subjects are told in advance that there will be two time periods during which they will receive either placebo or active drug. For example, in a study of flushing in women who were told there was a crossover design, the first half of the study produced similar significant improvements from both clonidine and placebo. However, in the second half of the study, there was a clear loss of placebo effect with the active drug group reporting significantly better improvement in symptoms compared to the placebo group[30], yet clonidine has been shown not to be effective for this symptom. Crossover trials are also problematic for studying placebo effects because of potential effects related to learning, and on expectancy when placebo follows active drug[31].

Non-blinding is a potential confounder for many agents acting on the central nervous system (CNS). An older systematic review of trials for tricyclic antidepressants (TCAs) suggested that the efficacy of TCAs was greater when compared against a completely inert placebo than when compared against a probably inactive agent for treatment of depression that produced similar side-effects to those of the TCA, i.e. atropine. The TCA group was better than the control group in only one of seven atropine controlled trials, while TCA was better than an inert placebo in 43 of 68 trials[32]. There are other potential differences in the studies, but they do raise the question of inadequate blinding of the control group impacting placebo responsiveness. Many subject biases with treatment are described below because they enter more into the realm of what most would consider part of the placebo effect (e.g. color of pill and branding).

Clinician biases may be present and range from quite overt to very subtle. On the overt end of the spectrum, clinicians who strongly advocate a new procedure for a disease often have significantly positive results. A systematic review analyzed five treatments that were later abandoned as being ineffective. During the initial published, uncontrolled trials of these treatments, response rates were often quite high. Proponents of these ineffectual procedures initially reported 40% excellent, 30% good and 30% poor responses[33]. New procedures or drugs are initially heavily advocated by clinicians but the interventions may have decreased efficacy over time. For example, the healing rate for cimetidine across over 50 controlled trials for peptic ulcer disease began decreasing in the 1980s while the response rate to a newer agent, ranitidine, remained stable across trials in the

same time period[23]. On the subtle end of the clinician bias spectrum is a study where subjects following a third molar dental extraction were told they would receive intravenous fentanyl, placebo or naloxone. There were two time periods for the study, one when the clinicians were told there were the three arms and the other where the clinicians were told there were only two arms, naloxone and placebo. The only difference in the placebotreated subjects for these two time periods was the clinical staff's knowledge of the study design. Patients receiving placebo had more pain relief when their clinicians thought they were in a three-arm trial possibly getting fentanyl than when the clinical staff thought they were only in a two-arm trial with just placebo and naloxone[34]. Another study of the placebo analgesic response following dental extraction found differences in the analgesic effect in subjects who received morphine by hidden infusion administered by a person in an adjacent room and subjects who received morphine injection by a preprogrammed infusion pump. The precise cues that patients may have perceived that caused these differences could not be identified[35]. Clinicians may also have expectancies related to disease or condition that could alter the reliability of clinical rating scales[36].

Placebo arms in clinical trials may contain some treatment. This is a greater issue in non-drug treatment trials. Use of sham acupuncture may elicit some of the same physiological responses as usual acupuncture. Placebo arms in antidepressant drug trials may receive some counseling. Placebo arms in many clinical trials have some clinical interactions that may include explanations for the illness. As noted above, simply being in a study may actually be a treatment as it relates to the Hawthorne effect.

Another issue that relates to placebo effect and perhaps should be considered part of the placebo effect is self-efficacy. Treatment regimens that actively engage the patient to have some sense of control over their disease process may produce better outcomes than those that are less actively engaging to the patient. There are usually not adequate control groups for self-management therapies and studies that clearly differentiate positive expectancy from self-management are lacking[11].

Despite these many, significant confounding issues that cloud the literature on the placebo effect[26,27,37], it is clear from the studies described in this chapter that the placebo effect exists, and we even know some of the underlying neurobiological mechanisms. The ensuing discussion will include factors that influence the expectancy, such as aspects of the treatment, clinician-patient interaction and conditioning as well as possible mediators of the placebo effect (Figure 1).

## CLINICAL ASPECTS

Factors that contribute to placebo effects are presumably culturally dependent; the studies discussed here are predominantly from Europe and North America. A clinician in a white coat with a syringe may produce nonspecific beneficial effects in some people but presumably would not produce similar effects in a person living in a rural, undeveloped country who has never been exposed previously to either a white coat or a syringe.

## Factors related to treatment

There have been many factors related to aspects of the treatment that impact placebo effects. Much of the early literature centered around physical aspects of tablets and capsules[38]. Studies suggested that people's perceptions of pills were influenced by their color[39–41]. Other studies have suggested that capsules are perceived to be stronger than tablets[40,42] and possibly larger pills stronger than smaller pills[40]. These perceptual characteristics even vary by ethnicity[43]. The number of pills also influences perception of pill strength[39]. In a systematic review of 51 duodenal ulcer trials totaling over 3300 patients, the 4-week healing rate among those receiving placebo was 44.2% if placebo was given four times a day compared with 36.2% if given twice a day, and the difference was statistically significant[44].

In addition to physical factors relating to the placebo, the brand name or overt symbolic association may be important. In a study of 407 chronic headache sufferers, subjects were given aspirin or placebo dispensed in either a highly publicized brand name container or a generic bottle. As expected, subjects who received aspirin reported more decrease in headaches than those receiving placebo. Also, subjects receiving their medication in a brand name container did significantly better than those receiving medication in a generic container. This brand name benefit was observed in subjects who received placebo as well as those who received aspirin, and in subjects who were regular users of the name brand as well as those who were not[45].

Injections elicit a stronger placebo effect than oral medications and surgery is best of all in terms of eliciting placebo effects. An early paper on hypertension treatment found that parenteral administration of placebo had a greater effect than oral administration of placebo[46]. In a formal systematic review of sumatriptan trials including over 1800

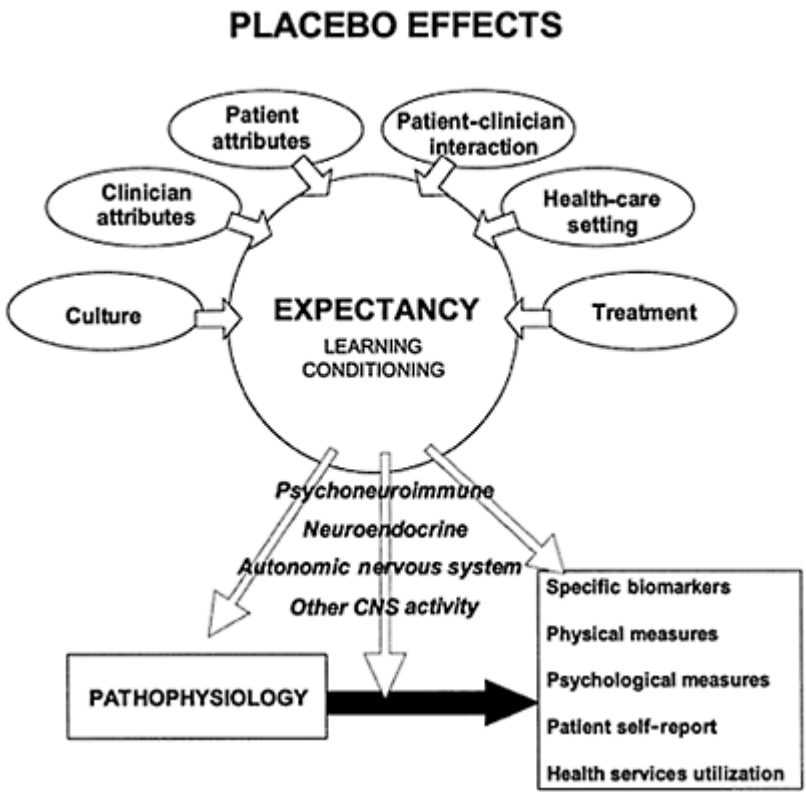


**Figure 1** Components of the placebo effect (or the meaning response) that alter expectancy, which then may affect the underlying pathophysiology or the health/outcome markers directly. These effects are possibly mediated through psychoneuroimmune, neuroendocrine, autonomic nervous system or other neural activities

patients, there was a higher response to subcutaneous placebo (32.4%) than oral placebo (25.7%), a statistically significant difference even after adjusting for several possible confounders including age, gender and headache severity[47]. There is a suggestion that medical devices may elicit stronger placebo effects than medications but, as Kaptchuk and colleagues concluded, well-designed experiments to evaluate this are not readily available[48].

While sham surgery is only rarely used, there have been several relevant reports. The whole issue of clinician biases, necessity of blinded trials and placebo effect was

dramatically raised by classic studies that evaluated internal mammary artery ligation for treatment of angina. After several publications and increasing clinical use of the internal mammary artery ligation, randomized, controlled trials were performed comparing the surgical technique of internal mammary artery ligation to simple incision and exposure of the artery without ligation[49,50]. The studies found no difference between the two surgical groups in the outcome measures and the procedure was abandoned shortly afterwards. One patient who had sham surgery reported 'Practically immediately I felt better… I figure I'm about 95 per cent better. I was taking five nitros a day before surgery. In the first five weeks following, I have had a total of twelve'[50]. In a recent trial of arthroscopic surgery for osteoarthritis of the knee, there was no difference in pain improvement between those getting actual procedures and those simply receiving incisions and sutures[51]. However, all three groups had a significant decline in their pain compared to their baseline. It had been suggested that 70% improvement in regular endolymphatic sac mastoid shunt surgery for Meniere's disease was secondary to a placebo effect, with the caveat that there was no natural history control[52]. In terms of Parkinson's disease surgery, the results are less clear, but there may be a significant placebo effect in this case as well[53]. There are ethical issues related to sham surgery as a control arm in clinical trials[54] but, despite objections by some[55], it appears reasonable to many researchers and oversight groups[56,57]. It could be argued that, given the potential benefit of sham surgery, the sham surgery should not be considered to have no potential benefit to the research subject, although this viewpoint would be controversial.

## Patient attributes

There are many factors related to the patient that impact on placebo effects. Issues related to culture and ethnicity will not be discussed here, but they have been written about[23]. It was thought for some time that only certain people experience placebo effects, but this was later felt not to be the case. More recently there have been a number of studies trying to determine whether personality or related traits in some way contribute to the placebo effect. While some studies have been negative[58,59], there have been other studies that have suggested that there may be some contribution. McNair and colleagues have shown that those who score high on the Bass Social Acquiescence Scale are more likely to demonstrate a placebo response to anxiolytic drugs[60–62]. The factor on this psychological scale that relates to placebo response is associated with agreeing with statements such as 'Obedience is the mother of success', 'The only known cure for fear is faith' and 'No gift is more precious than good advice'. The other personality traits that have been associated with placebo responsiveness are suggestibility or hypnotizability, and absorption, the degree to which one can focus on a single theme[63,64]. These data are also not consistent. In one study, subjects highly responsive to hypnosis had higher pain thresholds and pain tolerance during hypnosis, but there was no apparent effect of hypnotizeability on response to administration of placebo analgesic[65]. Anticipatory nausea and vomiting associated with chemotherapy is a meaning response and thus the mechanism may relate to the placebo effect. In one study of 70 patients, higher anticipatory nausea and vomiting was not related to trait anxiety, depression or gender, but was related to measures of absorption and autonomic perception[66].

Subjects more adherent to a placebo intervention did better than those less adherent to the placebo regimen in several studies with gross major medical outcomes, including mortality from cardiovascular disease and infections related to chemotherapy[67–69]. It seems unlikely that simply taking more placebo pills improves outcomes, so it is likely that subjects more adherent to a prescribed medical regimen have some different characteristic. Subject characteristics in these studies for which some statistical adjustment was attempted included severity in the case of the myocardial infarction studies, sociodemographic features (race, marital status and education), smoking and psychological characteristics (high lifestress, social isolation, depression and personality). Health-promoting activities that may correlate with adherence to placebo (or drug regimen) and are not easily corrected for statistically include diet, exercise and compliance with other aspects of medical intervention.

## Factors related to clinician and clinician-patient interaction

There are many aspects of the clinician-patient interaction that may produce improvements in clinical outcomes through some non-specific effects. Expectancy may be affected by the personal history of patient-clinician interactions and shared experiences of the patient and clinician as well as other context and white-coat effects[25,70].

The interaction with the health-care provider may provide non-specific benefits: stress reduction, decreased anxiety, or improvement of mood. It should be noted that alterations in mood, stress and anxiety may be conveyed by the intervention (e.g. pill) and not just by the examiner. Some clinicians are perceived to be better clinicians than others as a result of personality or interaction style. This may impact outcomes independently of any specific treatment. One of the earliest formal studies compared the success of the placebo used by different gasteroenterologists across several controlled trials for anti-ulcer medications. The average healing rate of patients receiving placebo in these trials across the four gastroenterologists ranged from 3 to 15 days, some of the differences being statistically different[71].

There have been other studies trying to evaluate the effect of some clinician personality traits or interaction style. In a study of analgesia for post-dental extraction pain, dental hygienists and dentists were instructed to be warm or neutral in their interaction style, i.e. engaging in more social conversation or not. The clinicians were also told to oversell or undersell the effectiveness of a pill to reduce anxiety and sensitivity to pain from the mandibular block injection. The pill was always a placebo in this single-blind experiment. The effect of overselling compared to underselling the placebo was highly significant on ratings of pain, anxiety and fear of injection. The interaction style had less but still a significant effect[72]. An earlier study evaluating responsiveness to an anti-anxiety agent in 138 patients in three clinical sites found significant effects on outcome when the clinician was more positive and enthusiastic about the medication compared to being less certain and experimental towards the medication. The effect was not simple with a complex interaction between drug condition (active or placebo) and clinician attitude that varied across the three clinic sites[73]. In another study, instructions prior to receiving a lactate infusion affected $p\mathrm{CO}_2$ and respiratory rate. Subjects who were told that the infusions may cause unpleasant bodily

sensations similar to those experienced during periods of anxiety had greater increase in respiratory rate and decrease in $pCO_2$ compared with subjects who were instructed that they would have feelings of pleasant excitement. This effect of instruction was only noted for the lactate infusion, although lesser trends in the same direction were noted for the placebo.

Diagnosis and diagnostic testing may impact clinical outcomes. One study randomized patients who had symptoms without major pathology to several groups. Subjects were given a firm diagnosis by the physician and told they would be better in a few days or the physician told them s/he was not certain what was the matter. Patients were also randomized to receive a prescription or not in each group. Patients who were given a specific diagnosis and told they would get better did in fact get better more frequently than those not given a diagnosis[21]. This same study found that, although giving a diagnosis had a significant impact, prescribing a drug as part of the management had no impact on outcomes. The ordering of diagnostic tests also appears to improve patient satisfaction and well-being. In a trial by Sox and colleagues, patients with non-specific chest pain felt not to be related to heart disease were randomized to receive no further testing or to have an electrocardiogram and creatine phosphokinase blood test. Patients receiving the diagnostic testing did significantly better in terms of their short-term disability and satisfaction with care[75].

The more often a patient is seen by a clinician, the greater the placebo effect. In a systematic review of placebo-controlled trials for ulcerative colitis, subjects in the placebo arms had significantly higher clinical, endoscopic and histological improvement rates when they were in studies seen more than three times by the clinician compared with studies where they were seen three or fewer times[76].

Clinicians who provide too many negative details of an intervention may elicit a nocebo effect. For example, in a small study of 28 subjects prior to lumbar puncture, of 15 subjects told they may expect to have a headache, seven did have a headache, while only one of the remaining 13 who were not told about a headache reported a headache[77]. In contrast, another study of 200 patients receiving new prescriptions for angiotensin-converting enzyme inhibitors, trimethoprim-sulfamethosoxazole, or non-steroidal anti-inflammatory drugs (NSAIDs) found no increased incidence of side-effects in the group receiving verbal and written information about the three most common side-effects compared with a usual-care control group[78]. It was unclear how much the usual-care control group was told about sideeffects.

## TRIAL DESIGNS AND THE PLACEBO EFFECT

Inert pills referred to as placebos are often used in double-blind randomized drug trials. The use of a placebo in such drug trials as well as other interventional trials has an effect on outcomes in part related to informed consent and subjects being aware of the possibilities. In routine clinical practice when patients are given a known drug, the effectiveness of the drug is a combination of a non-specific placebo effect and the biologically active effect. In double-blind placebo-controlled trials the effect of the drug is thought to be just the direct biological effect. However, since the placebo effect is not simply additive to the biological effect and the subject is aware that they are in a

doubleblind trial, conclusions from double-blind placebo-controlled trials are not straightforward[1,79]. In a double-blind trial, informed consent may alter the effectiveness of the placebo compared with the active agent in comparison to a situation where agents are administered without patients being given information concerning the study[80]. Doubleblind administration of decaffeinated coffee produced different effects on alertness and blood pressure than deceptive administration of decaffeinated coffee when subjects were told they were receiving regular caffeinated coffee[81]. There was a systematic review of trials in which NSAIDs were used in comparison with another active drug or in comparison to a placebo for treatment of pain in osteo- or rheumatoid arthritis[82]. In the trials in which the NSAID was being compared to a placebo, there was a significantly greater dropout rate related to ineffectiveness compared to the same NSAID being tested in an active drug comparison. On the other hand, patient dropouts were greater for adverse events in the trials in which the NSAID was compared to another drug than in placebo-controlled trials. Thus, given the same active NSAID, subjects had different experiences based solely on whether the other arm of the trial was a placebo arm or an active drug arm, despite the fact that the patient was not in that other arm but simply knew about it. In a smaller study where pain medications were given in a single clinical setting, there was a significantly greater benefit of the same NSAID when the drug was given as part of an active treatment-controlled study compared with a placebo-controlled study[83].

There are some data to suggest that placebo effects are greater for psychological and selfrated measures than other objective measures of disease activity[27]. A study that evaluated patients in placebo arms of rheumatoid arthritis drug trials found essentially no change over 6 months on the erythrocyte sedimentation rate but there was a significant improvement in articular index and morning stiffness[84]. While placebo responses may be generally greater for self-ratings, one study evaluating pain following bilateral third molar extraction found decreases in swelling and C-reactive protein following placebo ultrasound treatment (machine intensity set to zero) similar to the decreases found in self-reports of pain[85]. Another study observed elevation of liver enzymes in multiple dose trials during placebo treatment and attempted to determine predictors for those elevations[86]. Objective changes in pulmonary function in asthmatic adults have been observed following expectation of receiving an inhaled bronchoconstrictor[87,88] and these changes were reversed with expectation of receiving an inhaled beneficial drug. These placebo changes were not correlated with subject anxiety.[87]

The placebo effect has sometimes been considered as unfortunate noise while performing and analyzing data from randomized double-blind trials (see Kaptchuk for further discussion[1]). The response rate in placebo arms of 117 ulcer studies has varied from 0 to 100%, much more variable than the cimetidine or ranitidine response rates in the same systematic review[89]. In addition, there is often a significant correlation between drug and placebo healing rates across clinical trials[89], although this has not been completely consistent[90,91]. Some clinical trials in neurology have even begun excluding subjects if they demonstrate improvement in outcome measures during a placebo wash-in period[92]. However, there are many reasons for it to be beneficial to understand the placebo effect better, rather than simply ignoring it and excluding placebo responders from clinical trials. It would be beneficial to be able to define individual characteristics that correlate with the placebo effect; thus treatment arms in a randomized trial could be

better matched, improving the power of the study to determine the active treatment effect. Also, excluding subjects who have a greater placebo response may limit the possibility of seeing a therapeutic response, since these same subjects may show greater treatment effects as well.

Expectation plays a major role in subjective and behavioral effects of CNS-active drugs such as alcohol, amphetamine and related stimulants, caffeine and nicotine. This has been widely studied with the use of the balanced placebo design[93–95]. In the simplest balanced placebo design, subjects are assigned to one of four groups: subjects are either given active drug or placebo and either told they are getting active drug or told they are getting placebo. Much work in the field of drug abuse has utilized this experimental design. There are limitations to this design. While the balanced placebo design partially evaluates the differential effects of expectancy and direct pharmacology, it does not get directly at the placebo effect, in part because the placebo effect is not simply additive to the active or specific effect[96]. Also, when the drug effect is great enough, individuals become aware that they have been deceived if they have been told they received placebo but actually received a CNS-active drug[97]. Even with some weaknesses, the balanced placebo and other experimental designs can be used, at last partially to study the expectancy effects. Many psychopharmacology studies still do not address the issue of placebo or expectancy effect directly, and simply use the placebo administration as a control condition.

### Time course

It has been observed that a clinical response from a placebo may be less sustainable than a response from an active agent[98]. In one study of 55 patients with primary dysmenorrhea who had previously shown a response to placebo, subjects randomized to receive placebo had less sustained improvement than those randomized to receive naproxen or pirprofen. Those on placebo had a good response to the first cycle, the same as the active agents, but the beneficial response was not observed in later cycles, with the active agents clearly producing more benefit than the placebo for the next three cycles[99]. Quitkin and colleagues evaluated eight clinical antidepressant trials at their research clinic. Abrupt improvements in the first 2 weeks of treatment were unlikely to be due to the drug. These abrupt improvements had similar rates in the drug and placebo arms and were not sustained in either group. The improvements presumably more related to active drug effect as evidenced by differences in the two treatment groups were first noted in weeks 3–6[100].

## MECHANISMS

We will use the term expectancy as used in a recent Health Technology Assessment monograph concerning the role of expectancies in the placebo effect[11]. Expectancy related to placebo effect can be learned over short or long periods of time. Expectancies can produce specific changes in outcome such as anticipatory vomiting from chemotherapy[66] and dopamine release in the basal ganglia in Parkinson's disease[101]. Expectancies can also produce less specific and more subjective outcomes such as

general well-being and pain relief. It should be noted that even the less specific outcome of pain relief may be quite localized, e.g. to the left or right finger in the case of a study of placebo analgesic cream, and therefore is probably not mediated via non-specific global mechanisms such as anxiety reduction[102]. Expectancy of administration of amphetamine-like stimulant drugs may produce improvements in reaction time and mood[103–105]. How expectancies translate from thoughts into physiological processes is of great interest. The mechanisms underlying these expectancy effects may contribute to the self-healing promoted by many complementary and alternative medicine therapies and also to the effects of mind-body medicine.

Placebo effects presumably have multiple different mediators depending on the specific expectancy. The CNS is the primary location and mediator of the physiological basis of the placebo effect in its role in developing expectancies and through its outputs on sensory, motor and autonomic nervous systems as well as on the immune and endocrine systems.

Conditioning effects contribute to aspects of the response to placebo[106,107]. Many aspects of psychoneuroimmunology[108] may also contribute to aspects of the placebo response, both in its potential relationship to conditioning and in relationships mediated by stress that are affected by many facets of medical provider-patient interactions. Much of this work will only be very selectively reviewed in this section of the chapter.

In a series of studies, Ader and colleagues determined that an immunosuppressive effect could be obtained with placebo through conditioning. In a murine systemic erythematosus model, treatment with cyclophosphamide significantly increased the longevity of mice and time to onset of proteinuria. Some mice received cyclophosphamide on only 50% of their weekly injections. A group of these mice receiving only 50% of the dose were conditioned to receive the intraperitoneal injection of immunosuppressant following administration of saccharin solution. These conditioned mice had better outcomes than another group of mice who were given the same total doses of saccharin and cyclophosphamide but in a noncontingent manner[109] (Figure 2). Notably, the beneficial effect secondary to conditioning had disappeared by about 30 weeks. Even a commonly used clinical immune marker, the tuberculin reaction, can be significantly diminished through conditioning[110]. Highlighting the significance of conditioning in the treatment of neurological illness in humans, it has been

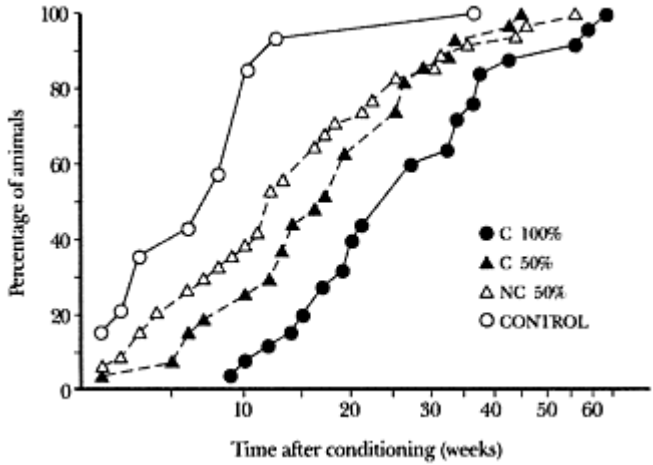


**Figure 2** Rate of development of proteinuria in a systemic lupus erythematosus mouse model receiving a weekly drink of saccharin and injection of cyclophosphamide (C 100%) or saline (control). The other two groups received half the amount of cyclophosphamide injections (the other half was saline). In the C 50% condition, the saccharin was given just prior to all the injections and in the NC 50% condition, the saccharin was administered in a non-contingent manner, i.e. on a separate day from the injection. Cyclophosphamide improved outcomes compared with those of control mice. Also, the mice who received cyclophosphamide on only 50% of the injections but were conditioned to expect it during the 50% saline injections, owing to its being contingently paired with a saccharin drink, did better than those who received the same doses of saccharin and cyclophosphamide but in

a non-contingent manner (precluding the development of any expectancy from the saccharin). Reproduced with permission from Ader R, Cohen N. Behaviorally conditioned immunosuppression and murine systemic lupus erythematosus. *Science* 1982; 215:1534–6

demonstrated that pairing cyclophosphamide treatment for multiple sclerosis with a gustatory stimulus (anise-flavored syrup) on five occasions resulted in the lowering of peripheral leukocyte counts in eight of ten subjects simply with administration of the anise-flavored syrup[111]. It is of note that four of ten experienced nausea following administration of only the conditioned stimulus, the anise.

Understanding conditioned responses is not straightforward, because of the presence of conditioned compensatory responses[112]. Siegel described a conditioned hyperglycemic response that was produced by rats that received an intraperitoneal saline injection instead of their previously given insulin injections. The time course of the hyperglycemia exactly mirrored the hypoglycemic response induced by the insulin[113,114]. While these conditioned compensatory responses are unlikely to contribute markedly to beneficial placebo effects, they may contribute to the non-specific clinical responses to the treatment provider and setting.

Expectancy learned over short periods of time, perhaps through conditioning, contribute to the placebo effect in humans[106,108,115–117]. For example, Voudouris and colleagues first administered a series of constantly intense, painful electrical skin stimulations. Next, application of a placebo analgesic skin cream was associated with either lowering or raising the intensity of the electrical stimulation. As might be expected, after 70 min of these conditioning trials, application of the inert skin cream lowered or raised the pain perception of an identical painful stimulus compared to the pre-conditioning trials, depending on whether, during the prior conditioning trials the intensity was lowered or raised during the application of the placebo cream[115,116,118]. Prior administration of caffeine produced increased alertness, assessed by electroencephalogram (EEG), and increased auditory vigilance when the subjects were later given placebo in what appeared to be conditioned effects[119]. In another study modeled on the Voudouris experiments, Montgomery and Kirsch added an additional arm to the study where subjects were told that the intensity of the electrical stimulation would be decreased in order to evaluate the effects of the supposed analgesic cream at lower pain intensities. The placebo effect was lowered in this condition, strongly suggesting that what had been considered a conditioned effect could be altered by verbally mediated changes in expectancy[120]. While some have argued that conditioning may not be used to explain these effects, since they were altered through verbal instructions, there is no inherent reason for conditioning not to be altered by other expectancies. However, perhaps the term ‘conditioning’ carries extra associations to some researchers, so the term ‘expectancy’ may be more neutral and thus better. An earlier study from the same researchers found that the placebo effect did not generalize to other body parts, strongly

suggesting that the mediator of this placebo effect was not some global mechanism such as anxiety reduction[102]. Another conditioning investigation with a similar design studied experimental heat pain. The researchers observed the expected placebo effect, but felt that it was highly correlated with subjectreported expectancy of pain and, interestingly, not with the desire for pain relief that was experimentally altered by instructions[121].

Prior exposure to an actual analgesic agent will impact a later placebo response. Subjects who received lower doses of propoxyphene reported lower analgesic responses to matched placebo the following day than subjects who received a higher dose of propoxyphene on the first day[122]. These researchers referred to the placebo effect as 'anticipation of analgesia' and it could come under the broad term 'expectancy'. While it may be important to distinguish clearly the placebo effects due to conditioning and expectancy, classical conditioning is interrelated with expectancy[24,120]. Other forms of conditioning, such as evaluative conditioning (the associative learning over time of likes and dislikes), also may play a critical role in determining preferences and expectancies[123] and thus contribute to the placebo effect.

There are many brain systems that produce relatively non-specific modulation of brain function. These systems include the non-specific thalamocortical and diffuse neurotransmitter projection systems arising from nuclei extending from the basal forebrain to the rostral pons. Any of these neurotransmitter systems may interact with the placebo effect. The norepinephrine (noradrenaline) system has been linked to orienting and attention[124]. The dopamine system has several elements that may be critical for the placebo effect. The dopamine system has some similarities to norepinephrine but is driven more by motivating components of appetitive events. It appears that dopamine may be critical in associating an environmental stimulus to the expectancy of a reward[125] as well as being released during behavior to obtain a reward[126]. It signals an expected reward through conditioning and learning. Dopamine release in the striatum was enhanced with a placebo dopaminergic agent in a group of Parkinson's patents as determined by positron emission tomography (PET) scanning (see below)[101]. The serotonin system is another relatively nonspecific projection system that may interact with the placebo effect.

The anterior cingulate is an important component of the dopamine system and has been activated during placebo analgesia[127]. The anterior cingulate may be critical in ongoing evaluation for action and error feedback[128,129]. Its activity is related to cognitive load or mental effort, especially during working memory tasks. The anterior cingulate may also be important for the motivating aspect or emotional significance of a stimulus. It has extensive connections with the limbic system. Additionally, patients with severe cancer pain benefit from a cingulotomy, because they develop a lack of attention or emotional response to the pain, not because they cannot perceive pain using standardized testing[130].

## CLINICAL CONDITIONS

### Pain

The pain system is the best-studied model of the placebo effect[98]. The opioid system is an important component of pain perception pathways and has been specifically related to the placebo response. Following removal of impacted third mandibular molars, the reduction in pain perception from an inert substance experienced by placebo responder subjects could be attenuated with administration of naloxone, while others without a placebo response had no change in pain when administered naloxone[35,131]. Placebo responders were defined as subjects whose pain decreased or stayed constant following administration of placebo compared to placebo non-responders whose pain continued to increase after administration of placebo. The latency of the improvement in pain ratings following intravenous administration of the inert drug was less than 5 min. Additionally, prior administration of naloxone reduced the probability of a beneficial response to the inert medication. In a later study from the same group, the response to an inert substance was greater in subjects who had higher initial pain ratings[132].

While naloxone may reverse the analgesia from inert agents, there is another component of the placebo analgesic effect that is not blocked with naloxone[133]. From more recent research it appears that only some of the placebo analgesic effect is mediated via opioid pathways and is blocked by naloxone. In an ischemic arm pain model in healthy humans, subjects were given either an opiate (morphine) or NSAID (ketoralac). These medications increased the duration that subjects were able to tolerate the pain. Improvement observed on the following day when subjects were given saline was presumably related to placebo effect. This improvement, postulated to be partially related to conditioning, could be blocked completely with naloxone following morphine days (Figure 3) but not following ketorolac[134]. In another study using the same experimental pain model, subjects were given either open or hidden injections of analgesic. Subjects had greater pain tolerance following open injection compared with hidden injections of analgesics[135]. The greater pain tolerance was associated with a significantly greater variability compared with the analgesic

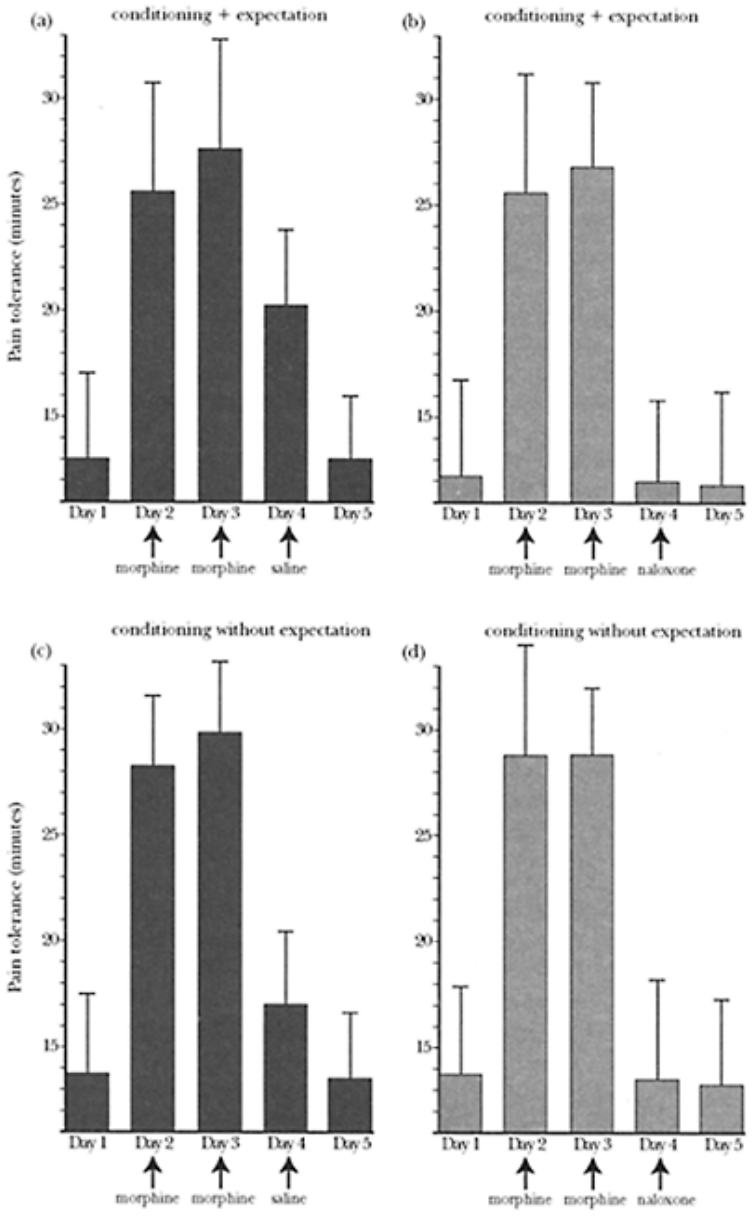


**Figure 3** Ischemic arm pain tolerance in healthy adults following baseline and 2 days of morphine injection. On day 4 saline or naloxone was administered to different subjects with

either the expectation that it was an analgesic (a, b) or without any expectation by being told it was an antibiotic (c, d) and a final day 5 without any injection. Naloxone blocked the analgesic response from the placebo saline condition following prior morphine exposure (b, d), but did not completely block the placebo saline effect following a similarly designed protocol using a non-steroidal drug analgesic instead of morphine (not shown). Reproduced with permission from Amanzio M, Benedetti F. Neuropharmacological dissection of placebo analgesia: expectation-activated opioid systems versus conditioning-activated specific subsystems. *J Neurosci* 1999; 19:484–94

response in the hidden administration condition. Administration of naloxone following open administration of ketorolac decreased the analgesic response to be the same as that following hidden administration, suggesting that the improvement in analgesic response in the open condition compared with the hidden condition was mediated through opioid pathways. The authors reached similar conclusions in patients post-thoracotomy who could not be given naloxone[135]. Open injection of analgesic produced greater pain reduction as measured by less need for on-demand analgesics than hidden injections. Additionally, the variability was greater in the open condition. This increased variability was quite prominent in these studies because the measure being evaluated, total analgesic dose required by the patients, was significantly lower in the open than the hidden condition but still had a greater variance. In some sense, responsiveness to placebo varied more across subjects than truly blinded (i.e. not knowing whether any medication was administered) response to analgesics. The same research group evaluated post-thoracotomy patients to evaluate response expectancies. Subjects given saline but told it was pain medication had significantly less need for analgesic medication than those not told anything. Subjects told they were in a double-blind study of a pain medication and had a 50% chance of receiving pain medication or placebo had a lowered need for analgesics, approximately half-way between the subjects not told anything and the subjects deceptively told they were getting an analgesic medication[136].

In addition to opioids, cholecystokinin has been related to the placebo analgesic effect. Cholecystokinin has a distribution in the CNS similar to that of the opioid peptides and

inhibits the analgesic effects of morphine. Proglumide, a cholecystokinin antagonist, has been shown to increase the placebo effect in an experimental pain condition (submaximum effort tourniquet technique)[137]. It is of some interest that this effect was seen only in placebo responders and that placebo non-responders had no change in pain with proglumide. Drugs altering cholecystokinin are related to placebo pain responses[138] but these are unlikely to be general mediators of placebo effects.

Positron emission tomography (PET) in healthy subjects during an experimental pain protocol was used to provide some information on cerebral localization of placebo effects. Opioid and placebo analgesia were both associated with increased activity in the rostral anterior cingulate cortex. This contrasted with greater activation in the caudal anterior cingulate cortex from pain. The spatial extent and degree of cerebral activation was much greater for the opioid effect than for the placebo effect. There were differences in activation between the high and low placebo responders, with the high responders having greater activation in rostral anterior cingulate and ventromedial prefrontal cortex[127].

## Parkinson's disease

People with Parkinson's disease often experience fluctuation in their symptoms as part of the disease process. With this fluctuation in mind, Goetz and co-workers[139,140] used a conservative definition of what would constitute a placebo response in a clinical trial of ropinerole: improvement in baseline score in motor Unified Parkinson's Disease Rating Scale of at least 50% or a change in at least two motor items at any one visit by at least two points. With this definition, one-sixth of subjects improved on placebo treatment. There was not a no-treatment control group in these studies. Also, the objective improvement on the Unified Parkinson's Disease Rating Scale was not related to improvements in subjective changes, raising the question of examiner biases. Such examiner biases in patients in clinical Alzheimer's disease trials have been noted in the negative direction with examiners[36]. In a systematic review of the placebo effect in Parkinson's disease, responsiveness to placebo did not relate to age, gender, religion, level of education or duration of the disease[141].

There has been an attempt to determine the brain mechanism for improvement related to placebo administration in Parkinson's disease[101,142]. Patients with Parkinson's disease had PET scans using [$^{11}$C]raclopride PET scanning without administration of any drugs and following blinded administration of placebo or apomorphine. Subjects receiving placebo demonstrated a significant decrease in raclopride binding in the neostriatum consistent with endogenous dopamine release Color Plate 2. The raclopride binding changes reflecting dopamine release in the caudate and putamen were approximately 20% and of similar magnitude to the changes observed following administration of levodopa or apomorphine. Motor testing was not performed, since it would alter the PET scanning, and so it is unclear how the PET results directly relate to motor improvements.

## Depression

Placebo effects have been a significant concern in evaluating depression treatments for decades. There has even been a gradual increase in the percentage of depressed subjects

responding to inert drugs in the placebo arm of antidepressant drug trials[143]. The increase in response to placebo as measured by the Hamilton Rating Scale for Depression score has increased from about 20% to 35% over the past 20 years. This meta-analysis did not find obvious factors related to severity or earlier diagnosis that may have contributed to this change over time.

The large response to placebo, albeit related at least in part to natural history, has caused difficulty interpreting some clinical trials. A large clinical trial studying hypericum (St. John's wort) for its utility in treating moderately severe depression concluded that hypericum was not significantly better than placebo[144]. However, this same paper found no advantage of selegiline over placebo in the primary outcome measures, letting one conclude that placebo was quite effective in this study, although alternative conclusions are possible[145].

There has been an attempt to define the brain changes that relate to placebo responsiveness in depression. Changes in brain glucose metabolism using PET were similar in patients responding to placebo and to fluoxetine for treatment of depression. The overlapping brain regions included increases in prefrontal, anterior cingulate, premotor, parietal, posterior insula and posterior cingulate, and decreases in subgenual cingulate, parahippocampus and thalamus. Fluoxetine response was also associated with additional subcortical and limbic changes[146]. In another study, two 9-week placebo-controlled trials of fluoxetine and venlafaxine produced approximately equal numbers of responders (medication or placebo) and nonresponders (medication or placebo)[147]. Using cordance, a quantitative EEG analysis technique developed by Leuchter and colleagues, the researchers observed differences in frontal EEG between medication and placebo responders in contrast to the previously mentioned PET study. In both of these studies, the placebo arm contained some intervention, either the therapeutic milieu and group sessions of an in-patient psychiatry service or brief sessions of supportive psychotherapy.

Studies have evaluated predictors of response to placebo effect in depression. A formal meta-analysis suggested that non-suppression of cortisol on a dexamethasone suppression test predicted a poorer response to placebo[148]. Duration of a depressive episode lasting more than 1 year has also been associated with a lower response to placebo[149]. Other predictors of a better placebo response in depression, which may simply reflect milder disease with better natural history, include a lower Hamilton Rating Scale for Depression score and being married. There was no correlation between placebo response and duration of disease[150].

## Multiple sclerosis

There is a significant interaction between the brain and the immune system[108], and thus there is a potential mechanism for a placebo effect in multiple sclerosis, a neuroimmunological disorder. Some intervention studies have had more than one assessment prior to beginning active treatment, so the placebo effect can be partially evaluated by comparing the placebo treatment data to the baseline period data. Two examples are described here. The placebo control group in one interferon β-la study had a 20% decrease in magnetic resonance imaging (MRI) lesion number compared with the baseline period[151]. In another interferon β-la trial with just a single baseline assessment, there was also a placebo group improvement in MRI, as assessed by the number of

gadolinium-enhanced lesions[152]. However, given the unpredictable course of the disease, it is difficult to differentiate placebo effect clearly from natural history in the published multiple sclerosis trials.

## Epilepsy

Significant improvements in frequency of seizures, usually defined as a reduction by more than 50%, are not uncommon in placebo arms of anticonvulsant trials[153,154]. However, as with multiple sclerosis, the disease course is relatively unpredictable and no trials have directly evaluated the placebo effect with a natural history control. Most current anticonvulsant trials are add-on or comparison trials, so further data on placebo effect may be limited. There have been some proposals to initiate short-term placebo-controlled trials[155]. in which case it may be possible to estimate the placebo effect, provided a long enough pretreatment assessment was obtained for accurate estimation of baseline seizure frequency. Placebos have been used in epilepsy to induce psychogenic seizures, a relatively common problem in epilepsy referral centers. Patients with nonepileptic seizures of psychogenic origin may have their typical spells induced by saline injection, tilt table maneuver, or simple suggestion, but a high false-positive rate may preclude its routine clinical use[156–158].

## Aging and dementia

There are few data on the placebo effect related to aging. This is a very important area because of the changing demographics in the USA with the increasing percentage of seniors, and because seniors are the largest consumers of drugs. From a practical perspective there have been many placebo-controlled trials of memory-enhancing agents in older subjects. In some of the Alzheimer's disease trials there has been an improvement in performance during the first 1–2 months of a clinical trial[159] that has not been further evaluated. This shortterm improvement is perhaps related to learning effect, but some of the outcome measures are not sensitive to learning effects and the learning effect would be expected to carry over into succeeding test sessions. Thus, the short-term improvements may be related to placebo or expectancy effects. Often trials have an open-label extension. In some of these trials, the short-term improvement during the openlabel extension was greater than the improvement seen during the initial double-blind period of the study, again suggesting that placebo effects may impact some outcome measures in studies on Alzheimer's disease. Additionally, many patients with Alzheimer's disease in clinical trials who have received placebo fare better than those comparable patients reported from prior natural history control data. Although this may also be related to placebo effect, there are other explanations as well, including subject selection and Hawthorne effects related to attention and cognitive stimulation associated with participating in the study.

## CONCLUSIONS

There are factors related to a clinical interaction that may produce improvement in patient outcomes without directly affecting the underlying pathophysiology of a disease. Methodological artifacts such as regression to the mean and natural history have contributed to confusion about these factors. However, there are clearly effects on outcomes that are dependent on expectations of patients, whether these expectations are related to culture, previous interactions with the clinical setting, or conditioning. The biological basis of these effects are starting to be understood, especially in the realm of analgesic responses, but also in the realms of psychoneuroimmunology and neuroendocrinology. It will be helpful to understand the placebo effect from a biological basis in order to try to maximize health. It is likely that some therapies and therapists, both conventional and complementary, have been successful in improving people's health because of their utilization of these healing effects. Additionally, improving clinical trial design and interpretation will require a better understanding and characterization of non-specific healing responses comprising the placebo effect.

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# SECTION II: THE USE OF COMPLEMENTARY THERAPIES IN NEUROLOGIC DISEASE

# 13
# Headache

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*Complementary Therapies in Neurology: An Evidence-Based Approach*
Edited by Barry S.Oken
ISBN 1-84214-200-3 

The field of headaches has benefited from increased attention from the pharmaceutical industry. The serotonin agonist drugs of the sumatriptan type have revolutionized treatment of migraines and have dramatically improved the lives of millions of people. However, these drugs sometimes do not reach those who need them, do not work for at least 30% of patients, cause unpleasant side-effects in some and have the potential to cause serious sideeffects. Other treatments, such as botulinum toxin (Botox®) injections can be very expensive. These limitations lead many patients to consider complementary therapies. More than half of migraine sufferers do not even see a physician for their headaches[1] and many turn to a variety of complementary treatments, which are often cheaper, appear and usually are safer and are typically offered by practitioners with good bedside manners[2].

Headache is one of the most common complaints of patients seeing general practitioners and neurologists. The most common type is tension-type headache, which almost everyone experiences intermittently and which usually does not disable or reduce quality of life, unless it becomes chronic. The most common disabling type of headache is migraine. About 18% of women and 6% of men suffer from migraines, which means that over 28 million Americans have this disease. Migraines cause a significant effect on the quality of people's lives and can be severely disabling. Many migraine sufferers are misdiagnosed as having sinus or tension-type headaches and do not receive appropriate treatment. Some patients have both migraine and tension-type headaches and in some patients the diagnosis is not clear-cut. The general rule is that if a patient is found to have no structural or metabolic cause for her headaches and the headaches interfere with normal functioning, the most likely condition she is suffering from is migraine. Accumulating evidence indicates that genetic factors make people more susceptible to having migraine headaches. This genetic predisposition does not mean life-long suffering, since avoidance of triggers and non-pharmacological treatments can raise the threshold for migraines in the majority of patients and reduce or eliminate the attacks. Many non-pharmacological modalities can help several types of headaches, while others are specific to a certain headache type.

## MIGRAINE HEADACHES

### Elimination of triggers

Avoidance of triggers can dramatically reduce the frequency of attacks. An excessive amount of caffeine in the diet (for a headache sufferer, more than one drink a day) or in over-the-counter or prescription medications is one of the most common triggers. Some of the foods that can provoke migraine headaches include yogurt, bananas, dried fruit, beans, aged cheese, pickled and marinated foods and buttermilk. Monosodium glutamate and aspartame should be avoided. Among the alcoholic beverages red wine and beer are more likely to induce a migraine headache than vodka. Lack of sleep or excessive amounts of sleep (e.g. on weekends) can trigger a migraine attack in a susceptible individual.

### Nutritional therapies

Dietary approaches to the treatment of migraines are widely advocated and are in the category of complementary therapies but have very little scientific evidence. Tyramine-containing foods can trigger migraine headaches in susceptible individuals, as can skipping meals and some food additives and sugar substitutes. Some patients report that their headaches get better with elimination of wheat products, sugar or milk products from their diets. While we do not have scientific proof, it is possible to speculate on why these dietary changes may work. If the patient is so inclined there is no reason to discourage her from trying these dietary changes, which are usually safe and inexpensive. Strict vegetarian and other unusual diets can lead to vitamin $B_{12}$ and other deficiencies, which can make headaches worse and cause other problems.

### Biofeedback

Biofeedback is one of the therapies where definitive proof is difficult to obtain. Biofeedback is used by most of the specialty headache clinics; this does not prove its efficacy, but strongly suggests that a large number of patients benefit from it. Many clinical trials have shown effectiveness of biofeedback and relaxation techniques[3–7]. Results of these studies indicate higher response rates than those seen in placebo arms of prophylactic drug trials. Long-term follow-up studies suggest that biofeedback can have sustained efficacy for years after the completion of training[3,7].

The essence of biofeedback, which is often combined with behavior modification, is to teach a patient how to encounter stress without adverse physiological effects. A typical course of biofeedback consists of 8–10 weekly 30–45 min sessions. Learning to control one's physiological functions such as temperature or electromyographic activity can be achieved only by first learning to relax the skeletal muscles. This is achieved through progressive relaxation, visualization and breathing techniques. Most important, though, is the daily practice of these techniques. The practice sessions can be only a few seconds or minutes long, but they have to be very frequent. A conscious effort is required in the first

few weeks of training, but gradually self-monitoring and very brief relaxation techniques become a subconscious habit. This appears to allow many patients to lower tension throughout the day and this results in fewer headaches. Children are especially adept at biofeedback. They can often learn not only how to prevent their headaches in 4–5 sessions, but at times can learn how to stop their headache once it begins.

## Acupuncture

Acupuncture has been reported to be effective in the treatment of various pain syndromes, including migraine headaches. A consensus statement by a panel convened by the National Institutes of Health concluded that acute dental pain and nausea clearly have been proven to respond to acupuncture, while additional studies are needed for other pain syndromes[8]. A large number of animal studies have indicated that two mechanisms of action may be involved in acupuncture analgesia[9]. One is endorphinmediated and is naloxone-reversible, while the second is serotonin-mediated and is not naloxone-reversible. The two different types of analgesia can be induced by varying rates of electrical stimulation. Low-frequency (1–4Hz) stimulation induces naloxone-reversible analgesia, while high-frequency (10–100Hz) stimulation induces analgesia, which is not naloxone-reversible. Humoral mediation of the acupuncture effect was confirmed by a large number of studies, including an early study where cerebrospinal fluid from donor rabbits, which received acupuncture, raised the pain threshold in rabbits that were given this spinal fluid. Only about 60–70% of humans and animals respond to acupuncture. Patients with chronic headaches who did not respond to acupuncture were shown to have low endorphin levels[10]. Functional magnetic resonance imaging studies have shown activation of the periaqueductal gray area, which is active in pain transmission. However, placebo analgesia also activated this region.

Acupuncture treatment is carried out using very thin disposable needles, which cause very little discomfort or pain. Patients often fall asleep or feel very relaxed during correctly performed treatment. In patients with chronic headaches, treatment involves ten or more weekly 20-minute sessions. Electrical stimulation of the needles is sometimes used instead of the traditional twirling of the needles. When performed by a trained and licensed acupuncturist the procedure is safe. Side-effects of acupuncture are rare and include hemorrhage, bruising, pneumothorax and infection.

Double-blind studies of acupuncture are difficult to perform, because blinding for insertion of a needle is difficult, while inserting a needle into non-acupuncture points has been shown to produce a pain-relieving effect[11]. New techniques to mask needle insertion have been developed, and double-blind studies in various painful conditions are underway.

A review of 11 randomized controlled trials of acupuncture for headaches comparing true and sham acupuncture revealed that six trials showed statistical superiority of acupuncture and three showed a trend favoring acupuncture[12]. Therefore, while not fully convincing, the evidence suggests a role for acupuncture in the treatment of headaches.

Temporomandibular disorders (TMD) often coexist and contribute to migraine and tension-type headaches. A review of reports on the use of acupuncture in TMD found three randomized and blinded trials, and in all three trials acupuncture proved effective[13].

The duration of effect following a course of acupuncture varies from patient to patient. In some the relief is short-lived, while other patients obtain relief that lasts for many months. It seems unlikely that, in the presence of genetic predisposition and without reducing headache triggers, the effect of acupuncture can be very long-lasting. However, it is possible that a course of acupuncture that effectively controls headaches for the duration of the treatment may also reduce central sensitization and result in a sustained reduction of headaches after the course of acupuncture is completed.

In conclusion, despite the lack of definitive proof of its efficacy in headaches, acupuncture has a large supporting body of scientific research and a significant potential to help some patients with headaches. Issues of cost, convenience and patient preferences should be taken into account when deciding on this treatment.

## Physical approaches

Regular and frequent aerobic exercise as a treatment for headaches is impossible to study in a double-blind trial and would require a very large comparative trial to establish its efficacy. However, there is little doubt that it offers effective relief for many stress-provoked conditions, including headaches. Regular aerobic exercise may be effective for prevention of migraine headaches through several possible mechanisms. Exercise may not only relieve tension induced by stress, but it has been shown to improve blood circulation in the brain and may result in the release of endorphins.

Many migraine patients have neck muscle spasm, which is secondary to the head pain, and can precede or even trigger an attack of migraine. Strengthening isometric neck exercises are highly effective for patients with migraines. These exercises take very little time, but should be performed many times throughout the day if they are to be effective.

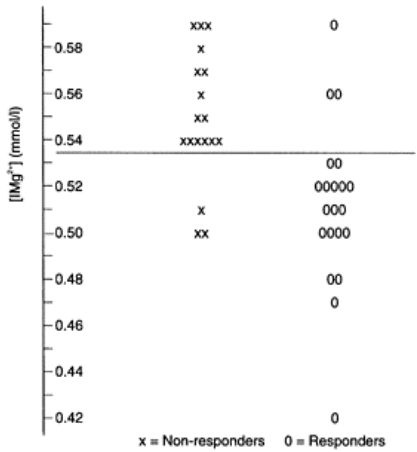


**Figure 1** Individual serum $IMg^{2+}$ levels and means in patients with migraine headaches before magnesium infusions

Other unsubstantiated but anecdotally effective modalities include application of heat and cold, massage and many other similar techniques. As long as they are safe and affordable, patients should not be discouraged from trying them.

Potential benefits of chiropractic manipulation should be weighed against the possible complications. While millions of chiropractic treatments are performed yearly with an excellent safety record, which is better than that of most prescription drugs, more than 100 cases of serious complications of chiropractic have been reported. Most of them are the result of neck manipulation resulting in a stroke. It can be safely assumed that a fairly large number of similar complications go unreported. Because there is no proof that this treatment works, and in view of the potential for very serious complications, it seems prudent to discourage headache patients from undergoing chiropractic treatment. Patients who insist on having this treatment should be advised to avoid having high-velocity manipulations, which are most likely to cause complications.

## Vitamins and minerals

Riboflavin or vitamin $B_2$ is involved in mitochondrial energy generation. Mitochondrial dysfunction is suspected to play a role in some patients with migraines. A double-blind study showed that riboflavin was effective for the prevention of migraine headaches[14]. The maximum effect was achieved after 3 months of daily intake of 400 mg of riboflavin. The study involved only 55 patients, but the treatment is benign and potentially effective, which makes riboflavin a good candidate for further extensive trials.

Magnesium is a vital element, which plays an important role in the pathogenesis of migraines. Many studies have found low magnesium levels in the serum and tissues of migraine patients[15–20]. Potential mechanisms by which magnesium can lower the threshold for migraines include such proven effects of lowered magnesium levels as vasoconstriction, reduced affinity of serotonin receptors and an easier activation of *N*-methyl-D-aspartate receptors. Stress has been shown to result in magnesium depletion, which suggests a possible physiological explanation for the role of stress in triggering migraine headaches. Other potential causes of magnesium deficiency are genetic factors, gastrointestinal disorders (e.g. irritable bowel syndrome, colitis), low dietary intake and almost any other chronic illness.

An intravenous infusion of 1 g of magnesium sulfate was given to 40 consecutive patients with an acute migraine[20]. Twenty-one patients had good and sustained relief of their headache. Of the responders, 86% had low serum ionized magnesium levels, while of the non-responders only 16% had low values (Figure 1). Oral magnesium supplementation was attempted as prophylactic therapy of migraines in four double-blind trials. Three of the trials showed positive results[15,21,22], while one had negative findings[23]. The negative study appears to have used a poorly absorbed salt of magnesium, which resulted in diarrhea in 45% of patients in the active arm, compared with 22% in the placebo arm. The incidence of diarrhea in the other three studies was under 20%. These trials along with other supporting evidence establish magnesium as a proven treatment for migraine headaches. One of these positive double-blind trials was carried out in children[22], while another one showed relief of menstrual migraines as well as premenstrual symptoms as measured by the Menstrual Distress Questionnaire[15].

Magnesium oxide, magnesium diglycinate and slow-release magnesium chloride appear to be well tolerated and well absorbed. The dose of magnesium for prophylaxis of migraines ranges between 200 and 400 mg of elemental magnesium.

A recent anecdotal report suggested that a daily dose of 150mg of co-enzyme Q10 could be helpful in preventing migraine headaches[24].

## Herbal remedies

Feverfew *(Tanacetum parthenium)* is the only herbal remedy that was submitted to several double-blind trials[25,26]. Fever few, when taken daily as a prophylactic therapy for migraines, was found to be better than placebo, but not dramatically effective. A review of these trials indicated a trend towards efficacy of feverfew over placebo[27]. A recent trial confirmed the efficacy of feverfew in patients with frequent (at least four in 28 days) migraines in a dosedependent manner[26]. Because feverfew is fairly safe and may help some patients, it is the herb to recommend to patients interested in herbal remedies.

Butterbur root *(Petasites hybridus)* is a toxic plant, but in a highly purified form it recently became available in the USA. It has been in use in Germany for the past 20 years. One doubleblind study (with several methodological problems) carried out in Germany showed that the highly purified extract of Butterbur root might be effective in the prevention of migraine headaches[28]. Another double-blind, placebocontrolled randomized trial was carried out in the USA and it confirmed the efficacy of this product[29]. Patients should be cautioned against using any Butterbur product other than the one used in these trials (Petadolex®) because of the toxic products that are difficult to remove. The available purified commercial product has been subjected to standard toxicology and teratogenicity studies and has been shown to be safe[30].

Guarana *(Pauillinia cupana)*, a relatively recent import from Brazil, is being used for headache relief. It may well have some analgesic properties because of its high caffeine content. However, daily caffeine consumption with a rebound phenomenon is one of the leading causes of frequent and refractory headaches. Guarana and all other caffeine-containing foods, drinks and medications should be avoided in patients with frequent headaches.

Anecdotal reports suggest that ingestion of ginger *(Zingiber officinale)*, ginkgo *(Ginkgo biloba)* or valerian root *(Valeriana officinalis)*, all of which are well tolerated, may help some patients with headaches.

*Aromatherapy* may not appear so far fetched if we consider how much of our brain is devoted to olfaction and that strong odors can almost instantly induce a migraine. A doubleblind study of healthy volunteers showed that an external application of *peppermint* extract raised the pain threshold and had musclerelaxing and mentally relaxing effect, while eucalyptus had a calming and relaxing effect and improved cognitive performance without an analgesic effect[31]. A study performed by the same group of researchers, using peppermint oil for tension headaches, showed positive results[32]. These studies give some scientific support to a variety of topical products being promoted for the treatment of headaches.

Homeopathy is based on an unproved concept of using infinitesimally small amounts of substances which in large amounts can induce symptoms that are being treated. Since

the treatment is extremely benign and relatively inexpensive it can be tried by patients who believe that it may help.

### Combination products

The overall efficacy of supplements in clinical trials, while significantly higher than that of placebo, is fairly modest. This can be due to the fact that some patients respond well, while others do not respond at all. Combining several supplements may increase the chance that one of the ingredients will help, and it is possible that they have a synergistic effect. MigraHealth® and MigreLief® are products that combine 300 mg of magnesium, 400 mg of riboflavin and 100 mg of feverfew.

## TENSION-TYPE HEADACHES

Biofeedback is one of the most effective treatments for tension[33] as it is for migraine headaches. Meditation, yoga and other mental exercises can help, but biofeedback is a more direct and a most time-efficient approach aimed at eliminating headaches. Well-trained staff and patient compliance with home exercises are essential for achieving a high success rate. Follow-up studies indicate up to 80–90% improvement 5 years after completion of a biofeedback course[4]. The treatment usually consists of 6–10 weekly 30-min sessions. Children can learn to rid themselves of headaches in as few as three to four sessions.

Acupuncture has a solid scientific basis confirmed in animal studies, but lacks the proof of large clinical trials. Acupuncture can stop an acute attack of tension-type headache or with a series of treatments relieve a chronic one.

Regular aerobic exercise is an excellent way to reduce adverse effects of stress on the body and it usually prevents headaches. Aerobic exercise can often relieve an acute attack.

## CERVICOGENIC HEADACHES

### Older patients

Cervicogenic headaches are more common in older patients and are usually due to osteoarthritic changes in the cervical spine. Pain described as radiating from the neck or occipital area suggests this diagnosis. Pain of cervical spine origin, however, can sometimes be felt in the front of the head. Decreased sensation over the occipital area, often on one side, can accompany occipital neuralgia. Neck muscles are tender, frequently in spasm, and their movement can aggravate the pain. In many patients, immobilization by a soft cervical collar during the night is sufficient to stop the headaches. More often, a combination of a non-steroidal anti-inflammatory drug with a cervical collar and regular isometric neck exercises will provide relief. Local heat application, transcutaneous electrical nerve stimulation (TENS) and acupuncture may be effective. In chronic cases biofeedback, massage and acupuncture can be useful.

### Whiplash injuries

Another frequent cause of cervicogenic headaches is a whiplash injury commonly sustained in car accidents. Treatment should include a soft cervical collar, which the patient wears only at night. Wearing the collar during the day for any length of time may cause atrophy of the neck muscles, which may in turn delay the recovery. If pain is severe, the collar can be worn around the clock for the first few days. An active exercise program is started as soon as the patient tolerates it. Local heat, acupuncture and biofeedback are effective as a part of the treatment of acute neck pain and the associated headache.

## POST-TRAUMATIC HEADACHES

In many patients post-traumatic headaches will subside in a few weeks or months without any treatment. Chronic post-traumatic headaches in many patients, however, are notoriously difficult to treat regardless of the presence or absence of litigation. Biofeedback, cognitive therapy, physical therapy with strengthening exercises and acupuncture can be effective in many patients. If headaches have migrainous features the treatments listed above for migraines can produce good results.

A supportive and understanding attitude is important in treating this condition, because of the frequent ineffectiveness of treatment and because of the associated neurological and psychiatric symptoms (memory impairment, dizziness, anxiety and depression).

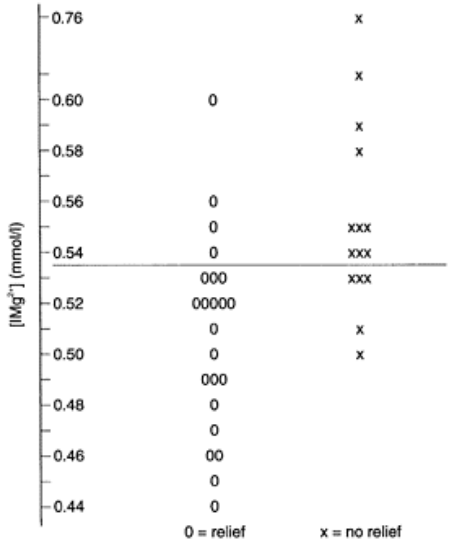


**Figure 2** Serum ionized magnesium levels in patients with cluster headache prior to magnesium sulfate infusions

## CLUSTER HEADACHES

Cluster headaches cause the most intense pain, which has led many patients to contemplate suicide. They are relatively rare and are often misdiagnosed in emergency departments and by primary care physicians as sinus or migraine headaches. Despite their extreme severity several non-pharmacological approaches can provide significant relief.

Melatonin, in a dose of up to 10 mg nightly, has been reported to relieve cluster headaches[34,35].

Inhalation of 100% oxygen through a mask at a high flow rate (8–101/min) is an effective abortive treatment for a large number of patients[36,37].

Repeated application of capsaicin has been shown to result in desensitization of the neurons through several possible mechanisms. These include inhibition of voltage-dependent $Ca^{2+}$ channels, neural dysfunction and depletion of substance P stores. However, it is not clear how this translates into relief of cluster headaches. When administration of capsaicin is stopped, it takes a month for local substance P levels to return to normal, while it takes 6–9 months for the restoration of normal sensitivity of neurons[38]. Several anecdotal reports and a double-blind study using intranasal administration of capsaicin ointment showed that administration on the ipsilateral side was more effective than if it was used on the contralateral side[39–42].

A study of intravenous magnesium in the treatment of cluster headaches suggests a possible 40% response rate in this difficult-to-treat disorder[43]. A correlation between clinical response and serum ionized magnesium levels was present in this trial (Figure 2) as it was in the trial in migraine patients. Oral supplementation may also help; however, because of the severity of this condition an infusion may be more appropriate for many patients, since this can provide immediate relief.

## CONCLUSION

Complementary methods of treatment often lack scientific proof of efficacy. This is also true for many drugs we use for prophylaxis of headaches. Many of the complementary methods are inexpensive, harmless and probably effective. The following is a list of options, in order of the author's preferences, that is presented to most patients with headaches: avoidance of triggers, regular and frequent aerobic exercise; isometric neck exercise; biofeedback or another relaxation technique, a combination product containing magnesium, riboflavin and feverfew (MigraHealth® or MigreLief®); and acupuncture. Patients are asked to decide which of these approaches are appealing to them and which they are likely to adhere to.

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# 14
# Complementary and alternative medicine treatment of back and neck pain

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*Complementary Therapies in Neurology: An Evidence-Based Approach*
Edited by Barry S.Oken
ISBN 1-84214-200-3 

## INTRODUCTION

Over the past decade, the awareness of the medical community has been raised regarding the extensive and growing utilization of what has come to be called complementary and alternative medicine (CAM)[1]. Eisenberg and colleagues[2] demonstrated an increase in the use of CAM therapies from 33.8% of the adult US population in 1990 to as much as 42.1% in 1997. Among those using CAM therapies, the probability of visiting an alternative medicine practitioner (as opposed to using a CAM therapy without a practitioner) increased from 36.3% to 46.3% during that same period. Over these 7 years, the total number of visits to alternative medical practitioners was estimated to have increased by 47.3%, with expenditure for alterative medicine services increasing by 45.2% to at least $27 billion in 1997. This figure is comparable with the total projected out-of-pocket expenditure for all US physician services.

Patients consult alternative providers for various reasons[3]. One of the more common reasons is a perceived limitation in conventional medical practice. Nowhere is this more obvious than in the management of back and neck pain, which exist in epidemic proportions in the Western world[4] and which, in most cases, have no completely satisfactory medical treatment. Therefore, many patients consulting CAM practitioners are doing so for back and neck complaints, with several CAM therapies being viewed as potentially effective for these conditions[5]. A recent study by Wolsko and associates[6] reported that, among those with back or neck pain, 53.6% had used a CAM therapy in the previous 12 months. Additionally, the percentage of patients who had consulted an alternative medical provider about their condition (34.1%) was almost equal to the percentage consulting a conventional medical provider (36.6%). Among the complementary therapies, the physical methods (chiropractic, massage, yoga, acupuncture, osteopathy) were the most widely used. Patient satisfaction with CAM therapies appears to be an important factor in their increased popularity, with 47.9% of patients with back and neck pain reporting that complementary methods of care were ‘very helpful’ for their condition, compared with 27.4% for conventional care[6]. The

CAM therapies with the highest perceived helpfulness were those utilizing physical methods, with chiropractic at 60.7% and massage at 64.9%.

## SCOPE OF THE REVIEW

Although many CAM therapies have been applied to the treatment of back and neck pain, this chapter focuses on those methods that are most commonly used and enjoy the broadest support in the literature, namely acupuncture, massage, mobilization and manipulation. We do not consider behavioral treatments (such as biofeedback or relaxation therapy), even though some practitioners consider these interventions to be 'alternative'. Following our review of the physical methods of CAM therapies, a brief synopsis will be presented on the use of nutritional supplements, homeopathy and magnets, which are often used by the public for back and neck pain.

## ISSUES IN COMPLEMENTARY AND ALTERNATIVE THERAPY RESEARCH

There are at least four main methodological barriers to overcome when attempting to study CAM therapies. The first is that most CAM therapies are in fact elements of broader healing systems based on a unique theoretical construct and system of analysis, rather than stand-alone treatments. To isolate a therapy (e.g. acupuncture) from its broader discipline (i.e. Chinese medicine) may neither do justice to that intervention nor reflect its true use by practitioners.

The second is that there is considerable disparity in the practice of these disciplines, a fact that is often overlooked by those outside a particular profession. To continue our example, acupuncture may be practiced in several distinct ways, with significant differences existing between Chinese, Korean and Japanese acupuncture. Even within each discipline there exist differences among practitioners in the type, number, or placement of needles, as well as variations in the frequency of treatment and use of adjunct therapies such as manual or electrical needle stimulation and use of herbal preparations orally or through moxibustion.

The third is that traditional outcome measures may not capture the full effect of a CAM treatment since many such therapies do not have well-recognized and understood physiological mechanisms of action (e.g. *qi* or *chi* Chinese medicine). In addition, many of the conditions for which CAM therapies are used (e.g. low back pain) are of a chronic nature and may not have easily measured physiological markers by which to gauge the effectiveness of a therapy.

The fourth is the question of the placebo effect (see Chapter 12). Because many of the popular CAM therapies are in fact physical methods (e.g. massage, acupuncture) of treatment, it is difficult to formulate a placebo that is both inert and indistinguishable from the real treatment. It is also difficult to differentiate the effect of the CAM treatment (e.g. massage) from that of the environment in which it is given (e.g. dark room with soothing music and aromatic oils). Certain patient—doctor interactions, such as the laying on of hands or the enthusiasm with which treatment is delivered, may be

particularly potent. Since blinding of CAM practitioners delivering a particular therapy is difficult or impossible, their enthusiasm may be lower when rendering a placebo treatment. Since a patient's expectations of benefit from a particular therapy may in part be derived from practitioner enthusiasm, patients receiving the placebo may have lower expectations of benefit. It has been reported that expectations of benefit can significantly influence the outcome of comparison trials of interventions for back pain, indicating that studies not controlling for expectation must be considered in this light[7,8].

Given these important barriers, the application of traditional epidemiological research methods devised for pharmacological studies (such as the randomized, placebo-controlled, double-blinded trial) to CAM therapies may be difficult. Although researchers are beginning to develop methodologies that are particular to CAM therapies, this process is only in its infancy and the results of these efforts may not be visible for several more years. Perhaps CAM researchers will eventually apply research methods similar to those used for surgical interventions (e.g. no blinding). These issues must therefore be considered when one reviews the CAM literature and attempts to draw conclusions regarding a particular therapy's efficacy.

## LITERATURE REVIEWED

This discussion focuses almost exclusively on the existing body of randomized clinical trials and, where available, on systematic reviews of a particular CAM therapy. Where no other literature is available, large case series are also discussed. Some CAM therapies have yet to be studied with regard to treatment of back and neck pain. These include aromatherapy, craniosacral therapy, reflexology, homeopathy and ayuvedic medicine. Therefore, these procedures will not be discussed any further.

Despite limitations, randomized trials remain the best available methodology with which to evaluate the potential efficacy of a CAM therapy for the treatment of neck or patients with back pain. Randomization deals effectively with the issue that a significant percentage of patients with back and neck pain improve spontaneously with time. The most obvious limitation to randomized trials in investigation of CAM relates to difficulty in the identification of appropriate placebo or comparison groups. Studies have utilized groups with several types of comparison, including comparison to conventional medical treatment, no treatment, patient self-education, or a devised sham treatment (e.g. non-thrusting light mobilization instead of manipulation), often designed to function as a placebo. In the last case, it is difficult to answer the issue of whether 'blinding' has truly been effective and whether the selected placebo is appropriate for the intervention that is being tested. Other trials have been conducted on a pragmatic basis, comparing two or more specific treatment approaches, one of which is a CAM therapy. Although this type of study may represent a good, 'real world' comparison, it cannot address the issue of relative placebo effects.

### Acupuncture

Although traditional Chinese medicine practitioners routinely use and recommend acupuncture to treat a variety of conditions, it has achieved its widest acceptance in the

West in the management of acute and chronic pain. Acupuncture has established some firm theoretical underpinnings in the systems controlling endogenous analgesia[9]. This has resulted in a large and growing body of research and has provided the basis for systematic reviews of acupuncture for pain[10], and in particular back pain[11–13], and neck pain[11,14].

There are several relatively distinct procedures that fall under the rubric of acupuncture. For example, there is traditional Chinese acupuncture that uses needles (among other methods) to affect energy flow along meridians. These treatments are applied according to unique methods of analysis (such as pulse diagnosis) and according to unique theories (such as the four-element theory and specific patterns of flow of energy, called *chi*). Other practitioners place needles based on a Western medical diagnosis or location of pain, while still other forms of practice use electrical resistance to determine the patterns of treatment. These other methods may or may not rely on the original theories or meridians or energy flow. There are several types of treatment that fall under the rubric of acupuncture. In addition to placing needles in a specific pattern, there may be specific patterns of needle movement, certain composition of the needles and even certain times of the day in which treatments are applied. Some use electrical stimulation, either through the needles or independent of them, or other methods of stimulating acupuncture points (including pressure or heat). There is no reason to believe that any one method is superior, but, similarly, there is no reason to accept that results derived from one method can be applied to other methods of acupuncture. The literature from

**Table 1** Summary of results from systematic reviews and meta-analyses of acupuncture for back and/or neck pain

| *Reference* | *Back pain (general)* | *Back pain (acute)* | *Back pain (chronic)* | *Neck pain (general)* | *Neck pain (acute)* | *Neck pain (chronic)* |
|---|---|---|---|---|---|---|
| Aker *et al.*, 1996[96] | | | | 0 | | |
| Ernst *et al.*, 1998[13] | +[†] | | | | | |
| White and Ernst, 1999[14] | | | | 0 | | |
| Smith *et al.*, 2000[11] | | | 0 | | | 0 |
| van Tulder *et al.*, 1999[12] | 0 | X | | | | |
| Kjellman *et al.*, 1999[97] | | | | 0 | | |
| van Tulder *et al.*, 2000[98–100] | | X | 0 | | | – |

| | | | | | | |
|---|---|---|---|---|---|---|
| Harms-Ringdahl and Nachemson, 2000[101] | | | | | X | |
| Henderson, 2002[102] | 0 | | | | | |
| Ernst *et al.*, 2002[103] | +[†] | | | | | |
| Kaptchuk, 2002[104] | 0 | | | | | |

Blanks indicate issues not addressed by the review. Where separate conclusions have been reached for acute and chronic pain, results are listed separately. +, finding in favor of acupuncture; −, finding of evidence against effectiveness; 0, finding of insufficient evidence to support benefit; X, reported inability to identify studies to address efficacy for the indication.[†], reported positive effects when compared to other treatments but no evidence of effect greater than placebo

systematic reviews of clinical trials is summarized in Table 1.

### *Acupuncture for back pain*

There have been a large number of studies and several recent systematic reviews of acupuncture for the treatment of low back pain (Table 1). In 1998, Ernst and co-workers[13] reviewed 12 studies of acupuncture for back pain and identified nine containing data that could be incorporated into a meta-analysis. These reviewers reported a significant advantage for acupuncture versus several comparison treatments. However, when the authors considered only the sham- or placebo-controlled studies, this advantage disappeared. They therefore concluded that there was insufficient evidence to determine whether acupuncture was superior to placebo for back pain.

Van Tulder and colleagues[12] also performed a systematic review of acupuncture for low back pain, assessing the methodological quality and outcomes of 11 studies. Because a variety of outcome measures were used, the authors decided against performing a meta-analysis and opted instead for a qualitative analysis. Overall, the quality of studies was found to be quite low. Findings were classified into four categories: strong, moderate, limited, or no evidence of effectiveness. The two studies of the highest quality showed no evidence of effectiveness for acupuncture. Furthermore, they found moderate evidence that acupuncture was no more effective than trigger point injection or transcutaneous electrical nerve stimulation (TENS) and some evidence that it was no more effective than placebo or sham treatment.

Leibing and co-workers[15] reached a similar conclusion in a study in which they randomized 131 patients with chronic back pain to physical therapy alone, physical therapy plus real acupuncture, or physical therapy plus a ‘minimal’ form of acupuncture. This ‘minimal intervention’ consisted of inserting needles just though the skin at sites 10–20 mm from the location of real acupuncture points. Both the real and sham acupuncture groups were substantially better than the group receiving physical therapy alone in terms of pain and disability, but no significant differences in pain or disability were found between these two groups either at the end of treatment or 9 months later.

Carlsson and Sjolund[16] randomized 50 patients with chronic back pain to conventional acupuncture, electroacupuncture, or mock TENS therapy (which they defined as placebo). Eight weekly treatments were administered, with two further treatments given over a 6-month period. Outcome measures included pain diaries, analgesic intake and activity levels. Blinded observers also subjectively assessed patients after 1 month, 3 months and 6 months. They reported a long-term beneficial effect of needle acupuncture in comparison to placebo.

Cherkin and co-workers[17] randomized 262 patients with predominantly chronic back pain to a maximum of ten treatments (over 10 weeks) of traditional Chinese acupuncture, massage therapy, or minimal intervention in the form of a self-education program on back pain. Follow-up was at 4 weeks, 10 weeks and 12 months. Massage was better than self-education in terms of disability and symptoms at 10 weeks and better than acupuncture in terms of disability at 10 weeks and in terms of both symptoms and disability at 1 year. Traditional acupuncture was not significantly better than either of the other interventions at any time point or on any measure.

Molsberger and colleagues[18] randomized 186 patients with chronic back pain who were undergoing conservative orthopedic treatment to receive acupuncture treatments, sham acupuncture or no additional treatment. They reported a significant benefit to acupuncture after 3 months, with 77% of the patients experiencing more than 50% improvement (compared to only 29% of the sham patients and 14% of the untreated patients).

### *Acupuncture for neck pain*

A systematic review by White and Ernst[14] in 1999 examined the results of 14 randomized clinical trials of acupuncture for neck pain, finding that they were equally balanced between positive and negative outcomes. In four out of five studies, needle acupuncture was not superior to a sham control. However, one study showed acupuncture to be superior to waiting-list control, leading some to question whether the sham control was indeed inactive. Additionally, acupuncture was equal or superior to physical therapy in three other studies. Five of the eight highest-quality trials were negative, leading to their conclusion that, although further studies are justified, there was insufficient support for recommending acupuncture for the treatment of neck pain.

Two additional randomized clinical trials of acupuncture for neck pain have been published since that review, both by Irnich and colleagues. In the first trial[19], they randomized 177 patients with chronic neck pain to 3 weeks of acupuncture, massage, or sham laser treatment. They reported a statistically significant advantage for acupuncture over massage 1-week post-treatment, but no difference between acupuncture and sham laser treatment. Subsequent statistical analysis of these data, however, argued for some effect above and beyond placebo for the acupuncture treatment[20].

In their second trial[21], the same authors conducted a randomized, double-blind crossover protocol of two types of acupuncture versus sham treatment in 36 patients with neck pain and limited cervical spine motion. The two forms of acupuncture included needling of distant sites and dry needling of local myofascial trigger points. The sham control consisted of laser treatments. The group treated with acupuncture at distant sites had a significant immediate improvement in motion-related pain and in range of motion,

while the local dry needling showed only a marginally significant immediate improvement in range of motion, with no change in pain.

### *Acupuncture summary*

Acupuncture is among the most widely studied of the CAM therapies for painful spinal conditions (Table 1). Despite some promising studies showing possible superiority of needle acupuncture over sham treatment such as laser therapy, there is a general opinion amongst scientists reviewing this literature that there remains insufficient evidence to determine its effectiveness for back and neck pain. Owing to the generally poor quality of studies, it has been recommended that future studies of acupuncture should focus on devising and employing an appropriate placebo intervention[22].

## Massage

Massage is the manual application of force to soft tissues of the body and uses a number of different techniques ranging from gentle rubbing of the skin (effleurage) to very vigorous forms of kneading of the deep tissues, as performed in Swedish massage. Additionally, some forms of massage (such as shiatsu) may be applied according to principles of meridianbased therapy, akin to acupuncture. With the exception of one study[23] that reported that acupuncture-based massage was better than Swedish massage, there is insufficient evidence to assess the value of one form of massage from another. For this review, all forms of massage are combined.

### *Massage for back pain*

A recent systematic review[24] evaluated eight randomized clinical trials of massage compared to several other forms of treatment for low back pain. The authors reported that overall, massage was superior to sham treatment, relaxation treatment, acupuncture and selfcare, and similar in effect to corsets and exercise therapy. Other studies suggested that massage was inferior to manipulation and TENS. Although the duration of observed effects was short in most of these studies, one study reported relative improvement at the 1-year follow-up[17]. The conclusion of this systematic review[24] was that massage might be beneficial for subacute and chronic low back pain. In some of the more promising trials, massage was particularly beneficial when combined with exercise and patient education, though the effect of each intervention could not be assessed.

Two recent studies of massage for low back pain were not included in this systematic review. Predye[25] randomized 98 patients with subacute low back pain (1 week to 8 months) to massage plus exercise, massage alone, exercise alone, or sham laser treatment. There were six treatments delivered over 1 month, with outcome measures (pain, function and range of motion) assessed at the conclusion of treatment and 1 month later. Both of the massage groups performed significantly better than the sham laser group, and the massage-only group was better than the exercise-only group at the end of treatment on the disability score (but not in terms of pain). As reported in other studies, the combination of massage and exercise was significantly better than either therapy alone.

In a study by Cherkin and colleagues[17] 262 patients with chronic low back pain were randomized in a managed-care setting to acupuncture, massage, or self-care educational materials. Patients were permitted to receive up to ten treatments of acupuncture or massage over 10 weeks. The main outcome measures included subjective symptom rating, overall health (SF-12), and disability (Roland Morris Disability Scale). After 10 weeks, massage was superior to self-care in terms of symptoms and disability and superior to acupuncture in terms on disability. At the 1-year follow-up, massage remained superior to acupuncture but not self-care. Other outcome measures were also supportive of massage. For patients assigned to the massage treatment group, the cost of subsequent care administered by the managed care organization was 30.5% lower than the self-education group and 44.8% lower than the acupuncture group, although this difference was not statistically significant, owing to a large standard deviation. The authors also included a measure of satisfaction and reported that 74% of patients rated massage as very helpful, compared with 46% for acupuncture, 17% for the self-education book and 26% for the self-education video.

### *Massage for neck pain*

There has been only one randomized clinical trial that specifically examined the effectiveness of massage for neck pain[19]. This study randomized 177 patients with neck pain to short courses of treatment with massage, needle acupuncture, or laser acupuncture. The group treated with acupuncture had slightly lower pain levels than both of the other groups 1 week post-treatment, though these differences disappeared after 3 months. Furthermore, the group treated with massage was no different from the group treated with laser acupuncture at any time point.

### *Massage summary*

The literature does provide some evidence that massage therapy may be beneficial for lower back pain at least in the short-term, and especially when combined with exercise and self-care education. Patient satisfaction with massage therapy appears to be high. Although massage therapy remains a widely used CAM therapy for neck pain, there is currently insufficient evidence in the literature for a proper assessment of its efficacy for this condition.

## Mobilization

Mobilization refers to the use of low-velocity mechanical or manual force that is applied to increase the mobility of a particular area, whether of a single joint (specific mobilization) or an entire body region, such as the neck or lumbar spine. There are several types of mobilization procedures that may differ in terms of the amount of force applied (very gentle versus rigorous), the frequency or length of application, the specific methods employed to produce the motion (small oscillations versus large movements), and their specific goal (neuromuscular rehabilitation versus breaking up of chronic fibrous adhesions). The motion applied through mobilization may be active (performed by the patient), passive (performed by the therapist), or a combination thereof.

Mobilization is often combined with other types of physical therapies such as traction, massage, or stretching. While there are several different ways to apply mobilization to neck and back pain, there is no reason to believe that one form of treatment is superior to another. Our review therefore combines all mobilization procedures, recognizing that future research may eventually elucidate differences between these various procedures.

### *Mobilization for back pain*

There is ample and growing evidence of the value of early general mobilization of patients with back pain[26]. However, as far as specific mobilization procedures are concerned, there is very little evidence that any provides a particular advantage in patients with low back pain. Much of this assessment arises from the fact that there are few studies that have employed mobilization as an independent or even primary intervention. For example, Hadler and associates[27] employed mobilization as a control procedure in a study of spinal manipulation. In this study, patients were randomized to treatment with a single manipulation or mobilization procedure. At 2–4 weeks post-treatment, manipulation was superior to mobilization in relief of back pain.

One of the better designed studies of physical interventions for back pain randomized 256 patients with chronic (i.e. longer than 6 weeks) back pain to one of four groups: treatment by physical therapists (exercises, massage and modalities); treatment by a general medical practitioner (advice about posture, home exercises and rest); treatment by a manual therapist (mobilization and manipulation); or placebo (detuned diathermy machine)[28,29]. Out come measures included severity of the main complaint, global perceived effect, pain and functional status. In the short term (12 weeks post-treatment), both physical therapy and manual therapy were superior to the medically treated group in terms of complaint severity and perceived effect, although there were no differences between the two approaches. At the 1-year follow-up, manual therapy was slightly superior to physical therapy in terms of complaint severity and functioning.

Another study[30] found that patients treated with the Maitland mobilization procedure per-formed no differently from patients given a regimen of exercises, corsets, or traction. However, this study examined patients with diagnosed radiculopathy rather than the non-specific chronic low back pain in previous studies. Although there have been several systematic reviews of mobilization therapy for low back pain, these reviews were combined with manipulation, with most of the discussion focusing on the latter treatment[31–33].

### *Mobilization for neck pain*

Several studies[34–38] have examined the effect of mobilization procedures on neck pain. These reports provide limited evidence for its effectiveness, particularly for short-term improvement in range of motion and reduction in pain. There is no evidence for improvement in functional status or disability and the duration of the effects of mobilization remains to be determined.

Very recently, two studies have made substantial contributions to the understanding of mobilization for neck pain. In the first study[39], 183 patients with at least 2 weeks of neck pain were randomized into three groups: weekly treatments of specific mobilization for 6

weeks; twice-weekly physical therapy sessions; and continued care by a general practitioner (analgesics, counseling and education). The principal outcome measure (percentage of patients reporting significant improvement or resolution of symptoms) was measured 1 -week post-treatment; pain scores and disability were secondary outcome measures. Mobilization was found to be significantly better than the other two methods of treatment in terms of recovery, pain and disability, although the difference in disability was fairly small. The authors concluded that manual therapy was a good option for the treatment of neck pain.

The second study by Hurwitz and colleagues[40] randomized 336 patients with neck pain in a managed care organization to one of eight treatment groups: spinal mobilization with and without heat; spinal mobilization with and without electrical muscle stimulation; spinal manipulation with and without heat; spinal manipulation with and without electrical muscle stimulation. Over the 6 months of observation, the treatment groups showed improvement over baseline in terms of pain and disability, with no statistically significant differences between groups. The authors concluded that spinal manipulation and mobilization were equally effective in the treatment of neck pain[40]. Because all patients received treatment, it is unknown whether the observed results were due to the treatment received or simply the natural history of neck pain.

### *Mobilization summary*

Mobilization procedures for neck pain have substantial literature support, appear to be significantly better than conventional medical management and compare favorably with spinal manipulation. However, it remains to be determined whether mobilization procedures are of benefit for low back pain, since there have been few direct studies of lumbar spinal mobilization procedures for low back pain and almost none in which mobilization was the sole treatment.

## Manipulation

Spinal manipulation is the application of force to a hypomobile joint through the use of a high-velocity, low-amplitude thrusting procedure aimed at moving a joint into its paraphysiological range of motion (see Chapter 3). There are several important issues that must be considered when reviewing this literature. The first is that, much like other medical therapies for low back pain, the methodological quality of the clinical trials has varied greatly from study to study[41]. Appropriate placebos for manipulative treatments are not well established and may be particularly difficult to validate. Most of the existing studies have therefore compared manipulation to other forms of therapy rather than to pure (i.e. no treatment) placebo groups. This has the potential effect of minimizing differences between groups. Additionally, there is significant variation in the delivery of manipulation amongst

**Table 2** Summary of results from systematic reviews and meta-analyses of manipulation for back and/or neck pain

| *Reference* | *Back pain* | *Back pain (acute)* | *Back pain (chronic)* | *Neck pain (general)* | *Neck pain (acute)* | *Neck pain (chronic)* |
|---|---|---|---|---|---|---|
| Ottenbacher and Difabio, 1985[107] | | + | 0 | | | |
| Koes, 1991[31] | 0 | | | | | |
| DiFabio, 1992[109] | | + | 0 | | | |
| Anderson *et al.*, 1992[106] | | + | + | | | |
| Shekelle *et al.*, 1992[49] | | + | 0 | | | |
| Koes *et al.*, 1996[62] | | 0 | 0 | | | |
| Assendelft *et al.*, 1996[105] | | 0 | 0 | | | |
| Hurwitz *et al.*, 1996[70] | | | | + | | |
| *Aker et al.*, 1996[96] | | | | + | | |
| van Tulder *et al.*, 1997[60] | | + | + | | | |
| Ernst, 1998[108] | + | | | | | |
| Bronfort, 1997[33] | | + | + | | 0 | + |
| Kjellman *et al.*, 1999[97] | | | | + | | |
| van Tulder *et al.*, 2000[98–100] | | + | +* | | | 0 |
| Harms-Ringdahl and Nachemson, 2000[101] | | | | | 0 | |
| Ferreira *et al.*, 2002[110] | | | + | | | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Gross *et al.*, 2002[69] | | | | | | 0 | |

Blanks indicate issues not addressed by the review. Where separate conclusions have been reached for acute and chronic pain, results are listed separately. +, finding in favor of manipulation; 0, finding of insufficient evidence to support benefit; *combined reports on manipulation and mobilization; †conclusion that positive effects were not clinically important; ‡only in concert with other interventions

practitioners without any knowledge of whether one form of manipulation is superior to others. For the purposes of our review all forms of manipulation are combined. The results of systematic reviews of spinal manipulation for back and neck pain are summarized in Table 2.

### *Manipulation for acute low back pain*

Spinal manipulation is the most commonly used CAM therapy for spinal complaints, with 53.0% of patients with low back pain and 57.4% of patients with upper back or neck pain reporting its use in the previous 12 months[7]. Manipulation is also the most studied method of treatment for low back pain, with approximately 39 published randomized clinical trials[42]. These studies have compared manipulation with various other treatments (e.g. medical treatment, self-education, etc.), placebo treatment (e.g. laser therapy) or no treatment in the management of acute, subacute and chronic low back pain. As a result of the positive results reported in most of these studies, several multidisciplinary expert groups and government guidelines[43,44] have included recommendations for the use of manipulation for uncomplicated low back pain. In addition to studies evaluating manipulation specifically, there have been several investigations that have compared treatment by various practitioners, including manual therapists[28,29], chiropractors[45–47] and osteopaths[48], with other forms of treatment.

Shekelle and colleagues[49] performed a meta-analysis of randomized clinical trials of manipulation for acute back pain in 1992. These authors computed quality scores for the clinical trials that had been published up to that time and identified seven (of the 58 that they reviewed) that were of sufficient quality and that had utilized standard outcome measures, thus permitting the data to be pooled. They analyzed the probability of recovery for each of the seven studies and found that manipulation increased the probability of recovery from acute low back pain within a 2–3 week timeframe by 0.17 (i.e. from 50% to 67%). This supported the conclusion that manipulation hastens recovery from acute uncomplicated low back pain. Furthermore, they found that none of the published trials had identified any serious complications of spinal manipulation for low back pain.

### *Manipulation for subacute low back pain*

Positive responses for manipulation have also been found in patients with subacute (4–12 weeks) low back pain. Hsieh and associates[50] performed a randomized clinical trial comparing manipulation with transcutaneous electrical muscle stimulation, massage or corset use. At 3 weeks, the manipulation group showed the greatest improvement in lumbar flexion and pain scores and reported the greatest patient confidence in their

assigned treatment. In another randomized trial, Blomberg and co-workers[51] demonstrated the superiority of a program of spinal manipulation, specific mobilization, muscle stretching, autotraction and cortisone injections over conventional medical care for industrial patients with acute or subacute low back pain. This benefit was seen in terms of pain, disability, sick leave and analgesic consumption, and persisted over the 90 days of observation. The effects of manipulation alone could not be isolated in this study, because it was part of a program that employed several interventions.

### *Manipulation for chronic low back pain*

There have been fewer studies examining the effects of spinal manipulation for patients with subacute and chronic back pain than for acute back pain. Gibson and co-workers[52] failed to show any significant effect in patients undergoing osteopathic manipulation, although Waagen and co-workers[53] showed a statistical benefit from manipulation in patients with recurrent or chronic low back pain 2 weeks post-treatment. Neither of these studies evaluated long-term outcome. In a crossover clinical trial using patients as their own controls, Evans and colleagues[54] showed improvement in chronic back pain in patients receiving manipulation and analgesics versus those treated with analgesics alone. Ongley and associates[55] randomized patients with chronic low back pain to receive spinal manipulation under sedation plus ligament sclerosing (proliferant) injections or saline injections. Both groups had improved significantly over baseline at the 1-year follow-up in terms of pain and disability, although the effect of manipulation alone could not be established from this study. Triano and colleagues[56] compared the use of spinal manipulation with a back education program in patients with chronic low back pain and noted greater improvement in pain and activity tolerance in the manipulation group. Bronfort and associates[57] studied the relative efficacy of three different protocols for management of chronic low back pain. These included 5 weeks of manipulation plus trunk strengthening exercises, a similar duration of manipulation and trunk-stretching exercises or supervised trunk exercises plus non-steroidal anti-inflammatory drugs (NSAIDs) followed by an additional 6 weeks of supervised exercise alone. Each of the three groups showed clinically important improvement, and there appeared to be a sustained reduction in medication use at the 1-year follow-up period in the manipulation and therapeutic strengthening exercise group.

As reported above in our review of mobilization, Koes and colleagues[28,29] randomized 256 patients with chronic (i.e. longer than 6 weeks) back pain to one of four groups: treatment by physical therapists (exercises, massage and modalities); treatment by a general medical practitioner (advice about posture, home exercises and rest); treatment by a manual therapist (mobilization and manipulation); or placebo (detuned diathermy machine). Outcome measures included severity of the main complaint, global perceived effect, pain and functional status. After 3 months, patients treated by manual therapists and physical therapists reported greater improvement in pain and disability than the other two groups. In follow-up evaluation 1-year post-treatment, improvement in pain and functioning was significantly greater in the manual therapy group than the physical therapy group. In an extension of this study[58], the authors reported the greatest relative benefit for manual therapy in those patients with chronic conditions (i.e. duration of 1 year or longer). Again, the effects of manipulation could not be isolated in this study.

More recently, Giles and Muller[59] randomized 77 patients with chronic (>13 weeks) spinal pain syndromes to one of three treatment groups: spinal manipulation; needle acupuncture; or NSAIDs. Outcome measures included disability (Oswestry Back Pain Index) and pain (Visual Analog Scale), and were measured at baseline and 4 weeks. After a median intervention period of 30 days, spinal manipulation was the only intervention to achieve statistically significant improvement over baseline. Pain reduction was 50% for low back pain, 33% for neck pain and 46% for upper back pain, while disability decreased 30.7% overall.

Van Tulder and colleagues[60] performed a systematic review of conservative interventions (including manipulation) for chronic low back pain. They found two high-quality studies that included a placebo arm, both of which reported an advantage for manipulation. They also identified eight studies comparing manipulation with various other treatments, with five of these showing an advantage for spinal manipulation. In none of the studies reviewed did the group treated with manipulation fare worse than those with a comparison treatment. They concluded that there was strong evidence to suggest that manipulation is more effective than placebo for chronic low back pain and moderate evidence that it is more effective than bedrest, massage or medical care as usual. This conclusion is similar to that arrived at by Bronfort[33], who also conducted a systematic review of the literature of manipulation for spinal pain.

In a more recent a systematic review of the literature, Ferreira and colleagues[61] have questioned the value of spinal manipulation for chronic low back pain. They reviewed nine studies, and pooled data from two placebo controlled trials and two comparative trials (with NSAIDs) in their data analysis. At a 1-month time point, they were able to show that manipulation had a statistically significant benefit when compared to placebo in terms of pain, and in comparison to NSAIDs in terms of disability (but not pain). Despite this statistical advantage, however, the authors gave the opinion that the difference was too small to be clinically meaningful. Another systematic review of the literature by Koes and associates[62] identified eight studies of spinal manipulation for patients with subacute or chronic low back pain, five reported positive results, two reported negative results and one had no conclusion. Overall, the methodological quality of the trials reviewed was low and this group of authors did not feel justified in concluding a benefit for spinal manipulation.

The Swedish Council on Technology Assessment in Health Care (SDU) recently published an evidence-based review on back and neck pain[63]. Their goal was to review the literature and formulate recommendations on surgical, psychological and conservative (including manipulation) care of the spine. In their evaluation of spinal manipulation for chronic back pain, they concluded that there was strong evidence for effectiveness of manual treatment/ manipulation in these patients.

The majority of the literature regarding manipulation for low back pain deals with uncomplicated pain of suspected mechanical origin. For more complicated cases of low back pain, such as those with sciatic nerve root involvement, there have been only two randomized clinical trials[30,64] assessing the efficacy of spinal manipulation. Both reported a significant short-term improvement for manipulation. Unfortunately, both of these studies were of low methodological quality, so there are insufficient data to determine the potential benefit of manipulation therapy in patients with sciatica.

*Manipulation for neck pain*

Although neck pain is the second most common indication (behind low back pain) for which manipulation is performed, there have been substantially fewer randomized clinical trials examining the effects of manipulation for this indication. Also, many of these studies have suffered significant methodological flaws. Therefore, it should not be surprising that the various systematic reviews of the literature on this topic have arrived at somewhat equivocal conclusions, with most declining to make firm conclusions, citing a lack of evidence. Nevertheless, 11 randomized clinical trials of spinal manipulation for neck pain have been published, with four of these trials demonstrating a positive effect for manipulation and seven having equivocal outcomes. Similar to low back pain trials, manipulation was never found to be less effective than comparison treatments or controls in any of the studies on neck pain. Based on the strength of this evidence, spinal manipulation was included in a short list of treatments recommended by the Quebec Task Force on Whiplash-Related Disorders[65] as being beneficial for short-term pain management.

Cassidy and co-workers[66] randomized 100 consecutive out-patients suffering from unilateral neck pain with referral into the trapezius muscle to receive either a single spinal manipulation or a single mobilization treatment (muscle energy technique). Fifty-two subjects were given cervical manipulation and 48 subjects received mobilization. There were no significant differences between the two treatment groups prior to treatment, in terms of either the history of neck pain or the level of disability as measured by the Pain Disability Index. The outcome measures were immediate post-treatment changes in pain and cervical spine range of motion. The results showed that both treatments increased range of motion, but manipulation had a significantly greater effect on pain intensity than mobilization. In the manipulation group, 85% of the patients reported pain improvement immediately after treatment compared to 69% in the mobilization group. The decrease in pain intensity was more than 1.5 times greater in the manipulation group, leading the authors to conclude that a single manipulation was more effective than mobilization for short-term relief of neck pain. However, since this study reported only immediate post-treatment results, no conclusion could be drawn as to the expected duration of these effects. There have been two other reports of an increase in cervical spine rotation and a decrease in neck pain following manipulation when compared with analgesics or no treatment[34,67].

Jordan and associates[68] randomized 119 patients with chronic (>3 months) neck pain to spinal manipulation, intensive neck rehabilitative exercises, or physical therapy. All three groups improved over baseline in terms of reported pain, disability, medication use, patients' perceived effect, and physician's global assessment, with no significant differences between the groups at the 4-month or 1-year follow-up assessments. Giles and Muller[59], on the other hand, compared spinal manipulation to needle acupuncture or NSAIDs in patients with chronic spinal pain syndromes (including neck pain). Spinal manipulation was the only intervention that achieved statistically significant improvements over baseline, with a 25% reduction of scores on the Neck Disability Index and a 33% reduction in neck pain as measured by the Visual Analog Scale.

Recently, several authors have attempted to analyze the literature regarding the use of spinal manipulation for patients with neck pains [31,33,69]. In 1996, Hurwitz and co-workers[70] published a review of the literature on the efficacy of cervical spine

manipulation and mobilization for the treatment of neck pain and headache. They reported that two of the three randomized controlled trials on patients with acute neck pain showed a short-term benefit for cervical mobilization. Three randomized clinical trials comparing spinal manipulation with other therapies for patients with subacute or chronic neck pain showed an improvement of pain at 3 weeks for manipulation compared to muscle relaxants or usual medical care. The authors concluded that cervical spine manipulation and mobilization probably provide at least short-term benefit for some patients with neck pain.

Gross and co-workers[71] examined 24 randomized trials and nine cohort studies of the efficacy of conservative treatments (drug therapy, manual therapy, patient education and physical medicine modalities) for patients with mechanical neck disorders. They concluded that, within the limits of methodological quality, the best available evidence supported the use of manual therapies in combination with other treatments for short-term relief of neck pain. More recent evaluation of the literature by these investigators[69] concluded that the evidence for manual therapy (including spinal manipulation) alone was not strong, but that there was evidence that these may be of benefit in concert with exercise therapy. Short-term benefits in acute neck pain have support in the literature, although the duration of these responses is unknown. Manipulation as an isolated intervention for neck pain has less literature support than do interventions incorporating a program of exercise and rehabilitation. It is also unclear whether manipulation is better than mobilization[40] or whether it is better in terms of outcome or cost than a program of intensive rehabilitation[68,45,72].

### *Manipulation summary*

Of all the CAM therapies for back and neck pain, spinal manipulation enjoys the broadest support base in the literature, with dozens of studies examining its efficacy and many systematic reviews evaluating this literature (Table 2). The preponderance of evidence argues that manipulation is beneficial for uncomplicated acute low back pain of 2–4 weeks' duration. Patients treated with manipulation appear to fare better than those treated by conventional conservative medical treatments, such as analgesics and self-education materials. The benefits of manipulation for neck pain are less clear. In the short term, manipulation appears to produce improvements in pain and range of motion in acute neck pain. The longer-term benefits of manipulation for neck pain are unknown. For both neck and back pain, the literature indicates that treatment programs combining spinal manipulation with stretching or rehabilitation exercises appear to offer a greater benefit than manipulation alone.

## OTHER COMPLEMENTARY AND ALTERNATIVE THERAPIES FOR NECK AND BACK PAIN

Although the physical methods of treatment reviewed above are the most commonly used and most researched forms of CAM therapy for neck and back pain, other CAM therapies have also been used in an attempt to alleviate these symptoms. These include laser

therapy, magnets, homeopathy and nutritional supplements. A brief review of each is presented below.

## Laser therapy

Low-power lasers have been used to treat several musculoskeletal conditions, including back and neck pain. The proposed mechanism of action is unclear, and various types of laser and application techniques or protocols have been suggested, including its application trigger points or acupuncture meridians. For our purposes, all laser treatments will be reviewed together.

### *Laser therapy for back pain*

Klein and Eek73 randomized 22 patients with chronic low back pain to exercise therapy in combination with low-energy laser treatment or placebo laser treatments. Pain and disability scores improved in both groups at the end of treatment and 1 month thereafter, but there were no significant differences between the active and placebo laser treatments. A study by Basford and colleagues[74] randomized 63 patients with musculoskeletal low back pain lasting over 1 month to treatment with active or inactive laser therapy. The active treatment group perceived significantly greater improvement and had more improvement in function, though there was no relative improvement in range of motion. These effects decreased with time, although the improvement in function was still noted at 1-month follow-up. The authors concluded that the observed benefits of laser therapy were small, despite their statistical significance, and recommended further investigation.

### *Laser therapy for neck pain*

There have been several studies[75–77] investigating the possible effects of laser therapy on neck pain. A systematic review of this literature[78], pooling data from three studies, found no significant benefit, although the authors noted that these studies had small sample sizes and were thus unlikely to detect small differences. More recently, Ozdemir and co-workers[75] compared outcomes in 60 patients with neck pain due to cervical spondylosis treated with active laser therapy or a control laser treatment. They reported a significant short-term improvement in the active treatment group, with no change in the control group.

### *Laser therapy summary*

There appears to be little support in the literature for the use of laser therapy for back and neck pain. The two systematic reviews[78,79] of this topic have concluded that there is insufficient evidence to support the use of low-power lasers in the treatment of musculoskeletal conditions, although the paucity of good studies indicates the need for further investigation.

## Magnets

The use of magnets to treat medical conditions dates back hundreds of years. More recently, there has been great interest in the possible use of magnets in the treatment of chronic pain[80] for conditions as diverse as fibromyalgia[81], arthritis[82,83], pelvic pain[84,] peripheral neuropathy[85], post-polio syndrome[86] or other localized musculoskeletal pains[87]. This interest has been fueled by both the popular press and numerous testimonials from well-known figures making claims for its benefit in wrist pain, foot pain as well as neck and back pain. These magnets may be applied to the body area directly or in the form of magnetic mattress pads, shoe inserts, bracelets, etc. Additionally, various techniques have been utilized, ranging from static magnetic fields, usually by way of magnets of relatively low field strength worn directly next to the body, to pulsed or highintensity treatment. There is no reason at the present time to believe that one procedure is more effective than another, however. Studies examining the potential effect of magnets on neck and back pain have only recently been attempted.

Collacott and colleagues[88] examined 20 patients with chronic back pain in a doubleblind, placebo-controlled, crossover pilot study of static magnetic therapy, with the magnet (or a placebo) worn for 6 hours per day for a week. There was a 1-week 'washout' phase and then the other therapy was applied. There was no significant difference in pain response between application of placebo and real magnet in this small study. Of course, this small study ran the risk of failing to detect a small change and the findings only apply to the particular magnetic parameters studied.

Thuile and Walzl[89] studied 100 patients with lumbar radiculopathy and 92 with headache and neck pain related to whiplash syndrome. The patients were randomized to 2 weeks of magnetic field treatment or control treatment that consisted of continued out-patient medication. The patients in the group receiving magnetic therapy showed significantly more improvement in terms of back and leg pain (lumbar radiculopathy) or headache and neck pain (whiplash) than the control group. However, placebo cannot be excluded as a major factor in this recovery, since therapy was not carried out in a blinded manner.

Magnetic therapy is only beginning to be investigated in a systematic way. One difficult problem with studies is potential difficulties with blinding of patients[84], particularly when employing magnetic devices that patients take home. The popularity of this treatment, combined with some intriguing albeit very preliminary investigations, should prompt more rigorous study before final conclusions can be reached regarding this popular treatment.

## Homeopathy

Homeopathic treatment entails the use of various compounds that are typically quite toxic in higher concentrations but have been diluted to such infinitesimally small concentrations as to be undetectable by modern equipment. This form of treatment is based on the concept of 'like cures like' and states that toxins that produce a particular set of symptoms will, in very small amounts, cure that set of symptoms.

Homeopathy is not generally considered to be effective in the treatment of back pain[90]. Stam and co-workers[91] conducted the only double-blind randomized clinical trial that appears in the conventional medical literature, comparing the effects of a homeopathic gel versus capsaicin cream in the treatment of acute low back pain in 161 patients. There was no difference in effect between these treatments, other than a higher prevalence of sideeffects with capsaicin. Both groups of patients improved, but without an untreated control group this study could not determine whether the effects were due to therapy, natural history or the placebo effect.

## Nutritional supplements

While some treatments with nutritional supplements can hardly be considered alternative (the use of vitamin D in patients with back pain due to osteoporosis, for example), most nutritional supplementation and herbal and botanical preparations are considered in this category. Various nutritional supplements have been recommended as beneficial for back and neck pain. These include certain minerals (especially magnesium), omega-3 fatty acids (such as fish or flax seed oil), herbs (such as valerian and kava-kava), and other traditional Chinese herbal medicines. Unfortunately, few of these treatments have been subjected to rigorous study. A popular nutritional supplement is glucosamine, which has been used (alone or in concert with chondroitin) in the treatment of certain arthritic conditions. However, the rationale for using it has been based on the theory that pain is caused by degenerative arthritis, which is unproven in back and neck complaints. Leffler and co-workers[92] performed a 16-week randomized, double-blind, placebo-controlled crossover trial of a popular combination of glucosamine, chondroitin and manganese in degenerative joint disease of the knee or low back. Although they showed significant improvement in patients with knee pain, they failed to show a benefit in patients with low back pain. However, the numbers were so small, that firm conclusions cannot be drawn.

Mauro and colleagues[93] performed a double-blind randomized, placebo-controlled study of intramuscular vitamin $B_{12}$ in 60 patients with chronic low back pain who were not deficient in vitamin $B_{12}$. They found that both the placebo and the treatment groups had impressive improvement in pain, disability and analgesic use, with a statistically better response in the group receiving the vitamin $B_{12}$.

Schrader[94] reported a double-blind, randomized placebo-controlled trial of 2 months of oral magnesium oxide supplementation in 60 patients complaining of chronic low back pain. There were no differences in outcome between the placebo group and those receiving oral magnesium. However, the author also noted that there was no change in tissue or blood magnesium levels following supplementation, leading to questions of compliance and absorption.

In one of the very few studies of botanicals for treatment of back pain, Chrubasik and associates[95] randomized 114 patients with an exacerbation of low back pain to receive willow bark or rofecoxib, an anti-inflammatory medication. They reported that both treatment groups showed similar improvement in pain, recovery of function and the use of other analgesics. Of course, this could be interpreted to mean that both were ineffective and the improvement was due to natural history or that the improvement was due to the placebo effect.

Despite the popularity of botanicals, herbal preparations and supplements for the treatment of pains, including back pain, remark-ably few hard data are available on which to base treatment decisions and advice to patients. Many more such studies will be needed before clear evidence-based guidelines can be promulgated for the use of these kinds of supplement for the treatment of back pain.

## CONCLUSIONS

There is a large and growing percentage of the population using CAM therapies for conditions, such as back and neck pain, that are poorly addressed by conventional medical practice. Owing to methodological difficulties associated with researching CAM therapies, such as isolation of therapies from broader healing systems, the lack of established physiological mechanisms of action, lack of available biomarkers to measure progress in chronic conditions and the difficulty in conceiving an appropriate placebo, attempts at validation of CAM therapy claims have been difficult. Those therapies that have been studied more extensively are the physical methods of CAM therapy, such as acupuncture, massage, mobilization and manipulation. These therapies, and especially spinal manipulation, appear to offer at least short-term benefits for neck and back complaints in terms of pain relief. Longer-term effects are mostly unknown. It also appears that these therapies may be most beneficial when combined with an exercise program, leading patients to adopt healthier lifestyles. Another group of therapies, including lasers, magnets, homeopathy and nutritional supplements, have insufficient evidence from which to draw conclusions.

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# 15
# Epilepsy

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*Complementary Therapies in Neurology: An Evidence-Based Approach*
Edited by Barry S.Oken
ISBN 1-84214-200-3 

Since approximately 25% of epilepsy patients remain insufficiently controlled by current conventional approaches[1], interest in alternative treatments is high. In addition, many epilepsy patients may try to pursue alternative treatment options to avoid the well-known cognitive side-effects of most anticonvulsant medications[2,3], which include sedation, psychomotor slowing and dyscoordination.

This review begins with a description of the use of complementary and alternative medicine (CAM) treatments for epilepsy in different cultural settings. Alternative concepts of epilepsy are described, since an adequate understanding of complementary and alternative treatments requires some knowledge about the underlying alternative rationale. The review concludes with an overview of the different therapeutic modalities used, and provides data on efficiency, as far as available.

## USE OF ALTERNATIVE APPROACHES TO EPILEPSY

The patterns of use of alternative approaches to epilepsy differ between developing countries and developed 'Western' countries. In developing countries, traditional approaches are often the primary source of health care, and in rural areas only a small fraction of the population will receive conventional Western treatment[4]. In developed countries, about 8–12% of epilepsy patients use alternative medicines or consult alternative practitioners[4,5].

### Developing countries and traditional treatments

In developing countries, the available information on the use of alternative treatments is from India, Sri Lanka and Nigeria. A survey of 1000 patients with epilepsy seen at a tertiary care hospital in India showed that 32% of patients had used CAM[6]. The most commonly used modality was ayurvedic medicine, either alone (43%) or in combination with other CAM therapies (38%). A small fraction of patients used homeopathy (12.5%). In a study of 207 patients seen at a rural epilepsy clinic in Sri Lanka[7], 45.9% had used alternative medicine and 6.3% believed the epilepsy had arisen from evil spirits and other

supernatural causes. Of the users of alternative medicine, 90.5% used spiritual healing methods, often in combination with Western medicine.

Among 265 epilepsy patients seen at a university teaching hospital in Nigeria, 71.7% used traditional medicine in addition to anticonvulsants[8]. All of these used some form of herbal therapy, and 61% of traditional medicine users also utilized some form of spiritual healing. The majority of spiritual healing methods were fasting and prayer or the use of holy water.

### Western countries

The use of alternative medicine by epilepsy patients in Western countries has not been well studied. Of 37 patients with a diagnosis of epilepsy seen at a university-affiliated neurology clinic in the USA, 8% used alternative medications[5]. In a survey of an unknown number of patients seen at an epilepsy clinic in Holland, 12% had visited an alternative healer at least once[4]. In this setting, the most common clients seeking CAM treatment for epilepsy were mothers of higher social class with a child with intractable epilepsy.

## ALTERNATIVE CONCEPTUAL APPROACHES TO EPILEPSY

Over the course of history and between cultures many different explanations for the etiology of epilepsy have been brought forward. For the scientifically minded reader, it is important to understand and acknowledge such alternative explanations of epilepsy, to reach an adequate understanding of complementary and alternative treatments. Similarly, practitioners of traditional or alternative medicine would benefit from the acknowledgement of the principles of evidence-based medicine. Both evidence-based and alternative approaches have their limitations, and a meaningful exchange requires mutual acknowledgement of the different basic assumptions.

The many alternative concepts of epilepsy might be grouped into two main categories. The first group of concepts is derived from a spiritual view of illness, and describes epilepsy in spiritual terms. The second group of concepts describes epilepsy in terms of an imbalance in body processes or body energy flow. Many alternative medical systems include a combination of both.

### Spiritual concepts of epilepsy

In many cultures, epilepsy has a long history as a ‘sacred illness’[9,10]. Possession by evil spirits was once considered the etiology of epilepsy in many cultures[9,11]. Theterm ‘epilepsy’ is derived from the Greek word *epilambanein,* which means ‘to be seized’, ‘to be taken hold of, or ‘to be attacked’[9]. In shamanic practice, e.g. with South American[12] or Siberian[13] Shamans, or in traditional African medicine[8], demons and evil spirits were originally not the stuff of superstition, but were experienced first-hand in visions[14], sometimes induced by ingestion or inhalation of hallucinogenic plants[15].

Exploring what he termed the ‘collective unconscious’, the psychologist C.G.Jung[16] described a similar entity as ‘the shadow’; the same was described by the anthroposophist

R.Steiner[17] as 'the double'. In these contemporary views, the 'demons' may be seen as impersonations of our dark side, of our shortcomings, fears, obsessions and irrational compulsions. The author of a popular book on alternative treatments for epilepsy knows from personal experience how these can trigger seizures and describes her own experience with epilepsy as 'A monster beside myself'[18]. Understanding 'demons' in this way, shamanic practices can be translated into contemporary counseling techniques[19].

Even to a bystander, the direct experience of an epileptic seizure is frightening. The patient's sudden loss of human interaction, which is replaced by automatic or sometimes violent behavior during a seizure, makes it appear as if the individual person known to his family or friends has been temporarily replaced by something foreign and seemingly inhuman.

Loss of the original living cultural context of spirituality has led to the degenerative phenomena of superstition and attachment of social stigma to epilepsy patients[9]. For an understanding of mind-body treatment approaches to epilepsy, the experience of epilepsy patients of being overwhelmed by a force outside their control needs to be considered. Loss of control over one's life due to fear of seizures which may strike at any time contribute significantly to the poor quality of life with epilepsy[20]. Strategies aimed at stopping seizures or recognition and elimination of seizure precipitants (see below) address this need and, if successful, may contribute to improved patient autonomy and well-being.

Strengthening patient autonomy by self-control is also a goal in anthroposophic medicine, a Western form of modern spirituality in medicine[21–23]. Epileptic seizures are seen as an indication that the body of a patient, or specific body organs, are resistant to incarnation by the soul. Specific exercises in therapeutic eurythmy (see below), a form of movement therapy, are designed to strengthen the patient's spiritual autonomy and make the body more receptive to the soul[24].

### Imbalance of body processes or body energy flow

In many alternative medical systems, herbs, homeopathic preparations or acupuncture are prescribed individually to address imbalances in the patients' 'constitution'. This refers to the more subtle aspects of the body organization, variously described as the flow of life energy or the balance between elements or different organs.

In traditional Chinese medicine (TCM), epilepsy *(Dian)* types are differentiated according to an excess of one of the five elements, for example, wind epilepsy *(Feng Dian),* or wet epilepsy *(Shi Dian).* Similarly, a distinction between excess of Yang *(Yang Dian)* or Yin *(Yin Dian)* as the polarities of life energy *(Qi)* is made. In addition, epilepsy is also described in terms of the organs which are thought to cause the disease, such as heart epilepsy *(Xin Xian),* liver epilepsy *(Gan Xian),* spleen epilepsy *(Pi Xian)* and so on[25].

For example, epilepsy can be described as caused by a constraint of the flow of life energy *(Qi)* in the liver. The liver burns off Yin which results in an excess of Yang, and the fire energy tends to rise from the liver to the head and brain. The principles for treatment then would be to 'expel the wind…expel the phlegms… calm the patient…bring down the fever… relieve the stagnation of food…activate the blood

circulation…energize the spleen…energize the kidney'[25]. For each activity, a specific herb or acupuncture point would be chosen.

In ayurvedic medicine, the theory of the three doshas describes imbalances in body function[26]. *Vata* is airy and governs all movement in the mind and the body. *Pitta* is hot and governs digestion and metabolism. *Kapha* is wet and governs all structure and lubrication. Epilepsy might be described as an excess of any of the three doshas and is treated with corresponding herbs. In ayurvedic treatment, great emphasis is placed on proper food and nutrition. Epilepsy is felt to be aggravated by eating the wrong foods (*rajas* and *tamas*) which 'disturb the mind', and by emotions such as passion, anger, fear, greed, grief, anxiety, agitation, etc.[26].

In homeopathy, the 'constitution' of a patient is determined from minute details of the symptoms or even his personality, and a specific remedy is sought whose profile corresponds best to the patient's symptoms[27].

In anthroposophic medicine, treatment aims to restore healthy interactions between the physical body, life forces ('etheric body'), soul ('astral body') and spirit ('ego')[21]. In addition, the 'constitution' of a patient is described as the balance between the chilling activity of the nerves and senses, the rhythmical activity of heart and lungs, and the warming activity of the metabolic organs. As described above, epileptic seizures may indicate an increased resistance of physical body and life forces against soul and spirit as an expression of an excess chilling activity of nerves and senses. Botanical or homeopathic treatments are chosen on the basis of the individual specifics of the constitutional imbalances[21].

## MODALITIES USED IN EPILEPSY TREATMENT

Corresponding to the two groups of alternative concepts of epilepsy, the CAM modalities used

**Table 1** Comparison of different approaches to epilepsy in alternative medical systems

| | | *Recommended interventions* | | |
|---|---|---|---|---|
| *Context* | *Explanation for epilepsy* | *Behavioral* | *Medicinal* | *References* |
| Old Greeks: Hippocrates, Galen, Areteus | sacred disease humors | ligature | | 9 |
| Africa, South America: Shamanic traditions | possession by evil spirits sacred disease | spiritual healing: fasting and prayers, holy water, exorcism | Mupiki and Kiki tree bark | 4,8,12,19 |
| Traditional Chinese medicine | liver blockage of energy flow *(Qi)* | acupuncture | *Zhenxianling* preparation *Qingyangshen* | 25 |

| | | | | |
|---|---|---|---|---|
| | emotional shock during pregnancy | | *(Cynanchum otophyllum)*<br>*Paeonia radix*<br>*Piper nigrum* | |
| Ayurvedic medicine | disorder of energy distribution (doshas)<br>suppression of emotions or sexuality | yoga meditation<br>amulets | Brahmi *(Herpestis monniera)*<br>Ashwagandha *(Withania somnifera)* | 26, 72 |
| Homeopathic medicine | personality profile *(simile similibus curentur)* | | *Argentum nitricum*<br>*Belladonna*<br>*Bufo rana*<br>*Zincum* | 27, 74 |
| Anthroposophic medicine | resistance of body organs to soul incarnation | therapeutic eurythmy<br>imbalanced weight exercises | *Arnica*<br>*Agaricus*<br>*Belladonna/Hyoscyamus*<br>*Cuprum*<br>*Viscum album* | 24, 73 |
| Behavioral methods | sensory and emotional triggers | protection from triggers<br>antistress strategies<br>seizure arrest | | 43, 44, 46, 48, 76 |
| Orthomolecular medicine | deficiency of vitamins or minerals | | zinc<br>taurine<br>magnesium<br>manganese<br>pyridoxine (Vitamin $B_6$) | 18 |

for epilepsy treatment may be grouped into two main categories: mind-body approaches and medicinal approaches. Mind-body approaches are used to address the spiritual aspects of epilepsy, and alternative medicinal approaches are used to address imbalances in body processes or body energy flow. Many alternative medical systems use a combination of both. Table 1 provides an overview of alternative concepts of epilepsy and the corresponding treatments used in the context of common alternative medical approaches.

**Table 2** Clinical trials of complementary and alternative medicine treatment approaches to epilepsy

| *Modality* | *Treatment* | *Type of control* | *Type of study* | *Number of patients (treated/ control)* | *Treatment group* | | *Control group* | | *Reference* |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | *Per cent seizure free* | *Per cent 50% responder* | *Per cent seizure free* | *Per cent 50% responder* | |
| Behavioral programs | life hygiene/sensory protection /seizure arrest | n/a | n/a | 23 | 35 | ~42 | n/a | n/a | 53 |
| | life hygiene/antistress strategy/counseling | n/a | n/a | 36 | 39 | 53 | n/a | n/a | 31 |
| | trigger protection/ antistress strategy/ counseling | n/a | n/a | 11 | 64 | 100 | n/a | n/a | 54 |
| | Contingent relaxation | Attention | Random | 5/11 | 0 | 80 | 0 | 0 | 55 |
| Biofeedback | slow cortical potentials | n/a | n/a | 18 | 33 | 62 | n/a | n/a | 41 |
| Yoga | word repetition meditation | wait group | random | 11/9 | 9 | 64 | 0 | 22 | 32 |
| | *Sahaj* yoga meditation | sham or wait group | random | 10/22 | 40 | 90 | 0 | 10 | 33 |
| Acupuncture | LR3, LI4, GV20 needling | sham | random | 15/14 | 0 | ~20 | 0 | ~18 | 67 |
| Botanical | piper/antiepilepsirine | placebo | random crossover | 34/34 | 15 | 53 | 9 | 32 | 71 |
| | *'Qingyangshen' (Cynanchum otophyllum)* | n/a | n/a | 32 | 31 | 87 | n/a | n/a | 70 |
| | herbal 'tablets' | AED: luminal | not described | 100/40 | ? | 84 | ? | 92.5 | 77 |
| | *Zhenxianling* | n/a | n/a | 239 | ? | 95.4 | n/a | n/a | 69 |
| Anticonvulsants | Levetiracetam | Placebo | random | 101/95 | ? | 39.8 | ? | 10.8 | 78 |
| Surgery | temporal lobectomy | wait group | random | 40/40 | 38 | ? | 3 | ? | 79 |

## Mind-body approaches

Mind-body approaches address the spiritual (or mental) aspects of epilepsy. The underlying notion is that, by strengthening autonomy and self-control of the patient, the unexpected and sudden overwhelming force of seizures can be overcome. The author of the Hippocratic treatise *On the sacred disease* probably implied the use of behavioral countermeasures in saying 'To abolish this disease, one must apply the element which is opposed to it, and not what is favorable and habituated'[28]. Following this principle, since the time of the ancient Greek Galen and Areteus, seizures have traditionally been interrupted by the application of ligatures to the first affected limb[9]. In the present, about 60% of patients have some spontaneous experience with discovering their own methods of interrupting the development of fullblown seizures from auras[29].

Another aspect of mind-body approaches is the identification of potential precipitants for seizures, combined with strategies or regular exercises to eliminate them. Seizure precipitants may be emotional (anger, stress) or sensory triggers (television, flashing lights)[30,31]. Regular exercises and changes in lifestyle, in turn, are thought to increase the autonomy and self-control of the patient.

Mind-body approaches to epilepsy require individual attention and are time-consuming. This may at least in part explain the small numbers of patients in the published efficacy studies. Nevertheless, the results appear encouraging and warrant further investigation.

### *Ayurvedic medicine: yoga*

The practice of yoga includes postures, breathing exercises and meditation. Of these, meditation addresses the spiritual aspects of epilepsy in the most direct way and appears to be capable of changing electroencephalogram (EEG) patterns[32,33]. The use of yoga for the treatment of epilepsy has been reviewed recently[34,35].

Among the few studies of yoga meditation for seizure control in epileptic patients, two randomized controlled trials have been performed. The effect of Sahaj yoga meditation on seizure control was assessed in 32 patients with idiopathic epilepsy[33]. At bedtime, with the feet dipped in warm saline water, patients practiced meditation with the goal of reaching a state of 'thoughtless awareness'. A control group was placed in the same environment and posture without the practice of meditation. Four of the ten treated patients became seizure free, with none seizure free in the control group (Table 2). Another study examined the effect of word-repetition meditation in 20 medically intractable epileptic patients[32]. For results, see Table 2.

### *Anthroposophic medicine: therapeutic eurythmy*

Therapeutic eurythmy is a movement therapy commonly used in the context of anthroposophical medicine[24]. Eurythmy was conceived as 'visible speech' and 'visible song', capable of expressing human inner experience in the form of movement. Therapeutic eurythmy exercises are intended to increase autonomy over the experience and expression of emotions. Becoming active rather than remaining passive in the area of consciousness and emotions may reduce stress as a precipitating factor for seizures. For example, eurythmy exercises for mental 'absence' might include vigorous crossing of

arms or legs to enhance wakefulness. Therapists report that such measures at times are successful in interrupting seizures. Clinical studies on the efficacy of therapeutic eurythmy for epilepsy have not yet been performed.

### *Biofeedback*

Biofeedback techniques for epilepsy are based on observations that several components of the EEG can be modified by conscious control[36]. Among these, training of the 'mu rhythm' obtained during motor quiescence has been described as the sensorimotor (SMR) rhythm in the biofeedback literature[37]. Low-frequency components termed 'slow cortical potentials' have been studied extensively by multiple authors[38–41]. The task required to produce a 'negative DC-shift' appears to be similar to a mental relaxation procedure. One-third of 18 patients became seizure free in a study by Rockstroh and colleagues[41] (see Table 2). Data from a controlled trial using the same procedure[38] were difficult to interpret and showed less impressive results.

### *Controlled breathing*

Deep diaphragmatic breathing is recommended in several behavioral approaches. Hyperventilation, for example, in anxiety, results in slowing of the EEG and is a common trigger for generalized forms of epilepsy. Decrease in arterial the $pCO_2$ resulting in decreased cerebral blood flow is the proposed mechanism for these effects of hyperventilation. Relaxed diaphragmatic breathing aims to achieve the opposite effect: to increase the seizure threshold by increasing $pCO_2$[42]. This is a common component of stress-reducing techniques and may be an important mechanism in generating a response in EEG biofeedback as well as in a relaxing meditation.

In a variant for small children, used by the Institutes for Achievement of Human Potential, a rebreather mask is used to increase $pCO_2$ and to reduce seizures. Efficacy has not been tested in a clinical trial.

### *Behavioral programs*

The most promising preliminary results in the behavioral treatment of epilepsy have come from comprehensive behavioral programs. In such programs, individually designed interventions are used. These are tailored to individual seizure-precipitating factors and the individual possibilities for seizure interruption. A good review of behavioral approaches has been provided by Wolf[43]. A well-written description of a behavioral program for adults can be found in reference 44. Successful behavioral programs for children have been developed and described by Dahl and colleagues[45,46] andSchmid-Schönbein[47]. Such programs generally use the following strategies:

(1) Reduction of non-specific seizure triggers by counseling for lifestyle modification and the reduction of emotional stress
(2) Reduction of specific sensory seizure triggers by suitable behavioral measures
(3) Interruption of seizures in the aura stage by suitable behavioral measures.

### *Lifestyle modification*

In a study of juvenile myoclonic epilepsy by Martinovic[31], the most frequent seizure precipitants (alone or in combination) were: sleep deprivation (87%), emotional stress (36%), watching television or video games (25%), none (23%), menstruation (17%) and alcohol use (6%). After lifestyle counseling, eight of 22 patients became seizure free in this study. Similar seizure precipitants are found in focal onset seizures[30].

### *Reduction of sensory triggers*

Strategies to ameliorate effects of sensory seizure triggers are based on the knowledge of specific triggers such as flashing lights. This has been accomplished by avoiding identified triggers, by designing protective strategies such as using sunglasses, or by exercises designed to desensitize the sensory modality in question. This approach has been most successful in treating patients with reflex epilepsy[48].

### *Aura interruption*

Behavioral measures to interrupt seizures include the presentation of alternative sensory stimuli in the modality of the usual aura, or by voluntary alternative movements in the area of the usual partial motor seizures. For example, for an aura of hand numbness the patient might make a fist before motor manifestations begin.

A classical case of the successful and complete cure of temporal lobe epilepsy by aura interruption has been reported by Efron[49,50]. The patient had temporal lobe epilepsy with an olfactory aura, which reliably generalized to a tonic-clonic seizure. The patient had 7–18 seizures a month and phenobarbital and phenytoin were ineffective. Presentation of an alternative olfactory stimulus reliably stopped the evolution from aura to generalized seizure, and with continued treatment even auras disappeared over the course of 6 months. Similar complete successes in other patients have occasionally been observed at the Bielefeld Epilepsy Center (P.Wolf, personal communication, see also reference 51).

In a study by Rajna and co-workers[52], 50% of 562 epilepsy patients experienced reliable warning symptoms before a seizure; 20% of all patients attempted to interrupt the development of seizures and 10% felt they had been partially successful.

### *Results from behavioral programs*

In a study from the Bielefeld Epilepsy Center in Germany, eight of 23 patients who rejected pharmacotherapy became seizure free over 4 years of follow-up[53]. In a study by Reiter and Andrews[54], seven of 11 patients became seizure free, and the other four patients experienced >90% reduction in seizure frequency. The design of clinical trials in this field is challenging; a well-designed randomized study (with only 18 patients) has been published by Dahl and associates[55].

## Medicinal approaches

### *Nutritional/orthomolecular*

*Magnesium* Decreased levels of magnesium can predispose to epileptic seizures, and obstetricians commonly use intravenous magnesium to control seizures in eclampsia[56]. However, there is no evidence of a beneficial effect of oral magnesium supplementation in epilepsy outside these indications. High doses of oral magnesium can occasionally cause diarrhea[44].

*Zinc* Zinc has been found to be synaptically released and to act as a neuromodulator in the hippocampus[57], a region of the cerebral cortex commonly implicated in partial epilepsy. While synaptic zinc release may increase in the course of epilepsy[58], it is not clear whether the complex actions of zinc result in protection from or enhancement of seizures[59]. In either case there is no evidence to date to suggest a role of zinc supplements in the treatment of epilepsy.

*Taurine* Taurine has inhibitory effects in the central nervous system, and evidence of decreased taurine levels in epileptic patients have been used to advocate its use as adjunctive treatment for seizures[60]. However, results have been variable, and the use of taurine in the treatment of epilepsy remains controversial. For some patients, high doses of taurine can lead to peptic ulcers[44].

*Pyridoxine* Pyridoxine (vitamin $B_6$) is necessary for the synthesis of the inhibitory neurotransmitter GABA, and is effective when seizures are due to pyridoxine deficiency[61]. There is no evidence that pyridoxine is useful in the treatment of other forms of epilepsy. High doses of pyridoxine can be dehydrating and can cause gait problems and reversible distal numbness[44].

### *Botanical*

The number of plants which have been used for epilepsy in various settings is large. In most cases, efficacy is unknown or not documented. The majority of the available scientific literature covers testing of herbs in animal models of epilepsy. Potential anticonvulsant or proconvulsant effects of herbal medicines were reviewed by Tyagi and Delanti[62]. A recent review by Nsour and co-workers[63] lists over 150 botanicals traditionally used for the treatment of epilepsy which have shown some promise in *in vivo* or *in vitro* studies. In contrast, the same review lists only four clinical studies, which have some methodological problems. Clinical studies are clearly needed to evaluate the efficacy of promising botanicals in clinical use.

In the following, only a few of the most commonly used or studied herbs and some which are of interest because of controversy are discussed.

*Ginkgo biloba* While *Ginkgo biloba* extracts are most commonly used for cognitive impairment, they are recommended by some for the treatment of epilepsy, owing to their tonic and possible antioxidant effects[18]. In contrast, a recent report describes two patients with epilepsy well-controlled by valproate who developed frequent generalized seizures about 2 weeks after beginning regular use of *Ginkgo biloba* extracts for cognitive

impairment[64]. More detailed information from clinical studies is needed to solve this controversy.

*Marijuana Cannabis sativa* is occasionally recommended for the treatment of epilepsy[18]. Gowers reported about its use in the 19th century and prescribed it himself sometimes[65]. The recent conflicting evidence regarding marijuana and epilepsy has been reviewed by Gordon and Devinsky[66]. They reported that animal studies showed both anticonvulsant and proconvulsant effects of the primary psychoactive constituent Δ-9-tetrahydrocannabinol (THC), and mild anticonvulsant effects of cannabidiol, the primary non-psychoactive constituent. Clinical data are inconclusive about the overall usefulness of marijuana for the treatment of epilepsy.

## Traditional Chinese medicine

### *Acupuncture*

Within the context of TCM, acupuncture aims to restore the flow of life energy *(Qi)* along the meridians of the body. Some acupuncture points recommended for the treatment of epilepsy are reportedly similar to those for aggression[4]. Kloster and colleagues[67] reported a well-designed randomized study in 39 patients with chronic intractable epilepsy. Acupuncture was applied by two professors of acupuncture from the Shanghai University of Traditional Chinese Medicine to the points LR3, LI4 and GV20 in addition to points indicated by individual TCM diagnosis. The study included a control group with sham acupuncture at points that were considered ineffective. No difference was found between the two groups (see Table 2). In a separate study with 34 chronic intractable epilepsy patients, no effect of acupuncture on quality of life as measured by the standard QOLIE-89 was found[68].

### *Zhenxianling*

Prescriptions in Chinese medicine are commonly a mixture of many ingredients. One example is *Zhenxianling*[69], which consists of herbal tablets including valerian, antelope's horn powder, human placenta and seven other ingredients, and also of a plaster placed on the umbilicus, which includes semen strychni, semen hyoscyami and *Cynanchum otophyllum* and five other ingredients. This prescription was used in 239 patients with 95.4% having a reduction in seizure frequency by at least 50% (see Table 2). Regarding the interpretation of such results I am cautioned by a Western practitioner of TCM that physicians in Chinese hospitals are under significant pressure to produce positive research results.

### *Qingyangshen*

Another herbal treatment for epilepsy in Chinese medicine is *Qingyangshen* prepared from the root of *Cynanchum otophyllum.* Kuang and co-workers[70] (Table 2) reported on the effects of *Qingyangshen* as an adjunctive treatment in 32 patients with grand mal seizures that were refractory to conventional treatment. Of the 32 patients, 28 showed at

least 50% reduction in seizure frequency within 1 month of treatment. After 2–9 months, nine patients became sei zure free.

### *Piper nigrum/antiepilepsirine*

Among other herbs, pepper is used in TCM to treat epilepsy. Antiepilepsirine (AES) is an isolation of a piperine derivative which has been identified as a probable active ingredient which is commercially available in China. AES was evaluated in a 6-month double-blind crossover clinical trial as adjunctive treatment to conventional anticonvulsants in 34 children[71] (see Table 2). During AES treatment, 18 of 34 had a response (seizure freedom or a reduction in seizure frequency of at least 50%) compared to 11 of 34 during treatment with placebo.

## Ayurvedic medicine

Ayurvedic medicines often contain a mixture of many different herbs, often composed on the basis of individual constitutional problems of the patient. Among other herbal preparations, such *as Ashwagandha (Withania somnifera), Brahmi ghrita* is recommended for epilepsy[72]. *Brahmi* is the Indian name for *Herpestis monniera* (also named *Bacopa monniera*), an herb that is otherwise commonly recommended for cognitive impairment. *Ghrita* describes the form of preparation, which in this case is a paste used as a supplement to food and includes *Acorus calamus,* pachak root and the root of *Canscora decussata* in addition to *Herpestis monniera*[72]. Unfortunately, information on the efficacy of *Brahmi ghrita* for epilepsy is not available.

## Anthroposophic medicine and homeopathy

### *Viscum*

Botanical extracts from *Viscum album* (mistletoe) have traditionally been used in Europe for the treatment of epilepsy and other conditions. Madeleyn[73] reported six cases of infantile spasms, one 9-year-old child and two adult patients with epilepsy, who became seizure free on *Viscum album* treatment. In addition to oral preparations, sterile injectable preparations are available from several companies in Europe and the USA, since mistletoe is widely used as an adjunctive treatment for cancer.

The practice of classic homeopathy does not entail the use of general remedies for specific conditions such as epilepsy. Instead, remedies are identified for the individual patient on the basis of similarity of symptoms or even the personality which matches the profile of remedies[27]. There are, however, some homeopathic remedies whose treatment profile includes symptoms such as convulsions, which are typically associated with epilepsy. Most of these remedies are also commonly used for epilepsy in the context of anthroposophic medicine. In the following, only a few examples will be mentioned.

### *Belladonna and Hyoscyamus*

These plants from the family Solanaceae contain the anticholinergic alkaloids atropine and scopolamine which in toxic doses can produce symptoms reminiscent of epileptic seizures. The same plants given in high dilutions are used in homeopathy to treat epileptic patients. Madeleyn[73] described five children with epilepsy who, in combination with other anthroposophic remedies, became seizure free with homeopathic dilutions of belladonna or *Hyoscyamus.*

### *Bufo rana*

A preparation made from the poison glands of toads is also used in homeopathy for the treatment of epileptic patients. Soldner and Stellmann[74] described a 3-year-old boy with Lennox-Gastaut syndrome who became seizure free after treatment with a homeopathic dilution (C200) of the *Bufo rana* preparation.

### *Arnica*

Preparations from this plant of the composite family have been used to treat epilepsy either in homeopathic dilution or in the form of a bath. Charette[27] described a 30-year-old patient with post-traumatic epilepsy who became seizure free after homeopathic treatment with Arnica (C6). Madeleyn[73] described a 7-year-old child with Lennox-Gastaut syndrome who became seizure free after using baths with arnica extract three times a week.

## SUMMARY AND CONCLUSIONS

Many alternative approaches to the treatment of epilepsy use some form of behavioral intervention combined with a medicinal treatment. This corresponds to views of the dual nature of epilepsy which affects both mind and consciousness as well as the body and its energy flow. Spirituality and concepts of balance in body energy flow are important elements of many alternative approaches, which contribute to their persuasive appeal[75]. The popularity of alternative medicine and many overlaps between different approaches may indicate that important aspects of epilepsy (and other illnesses) remain elusive to conventional medicine. It may be worthwhile to attempt to uncover and define the common truths that underlie many alternative concepts of epilepsy and provide the foundation for individual therapy.

Epilepsy affects every patient in a unique way. Alternative practitioners often respond to this by formulating an individualized diagnosis and treatment plan for each patient. Compared to other illnesses, the treatment of epilepsy by alternative methods is challenging, and a well informed individual approach may be essential for success.

The available information on the efficacy of the described therapeutic approaches is limited. A thorough review of the current literature produced 11 clinical studies, which are summarized in Table 2.

To facilitate comparisons across studies, a 50% responder rate (the fraction of patients who experienced at least a 50% reduction in seizure frequency) was calculated from the available data. To allow for comparison, two recent studies on the efficacy of a newer anticonvulsant and of epilepsy surgery are included at the bottom of Table 2. Many of the studies performed in developing countries did not meet the rigorous standards of clinical studies as performed in Western countries. Nevertheless, their results draw attention to potentially efficacious interventions for epilepsy. Most promising appear to be the behavioral interventions as well as some of the botanical treatments. Both deserve further study in clinical trials.

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# 16
# Cerebrovascular disease

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*Complementary Therapies in Neurology: An Evidence-Based Approach*
Edited by Barry S.Oken
ISBN 1-84214-200-3 

## INTRODUCTION

A stroke occurs when a blood vessel in the brain either is blocked by a clot (ischemic stroke) or ruptures (hemorrhagic stroke). The brain downstream from this vessel is damaged, owing to a lack of oxygen and the effects of increased free radicals and other toxic substances. Stroke is the leading cause of adult disability and the third leading cause of death in the USA with over 700000 cases annually. The only definitively proven therapy for stroke, tissue plasminogen activator (TPA), is only effective in the first 3 h after a stroke and is therefore given to less than 5% of stroke patients. Therefore, for the majority of stroke patients, traditional medicine has little to offer other than physical and occupational rehabilitation. In this chapter we will first review the potential benefits of complementary therapies, including acupuncture and hyperbaric oxygen, which may improve stroke symptoms and recovery. We then discuss selected supplements and vitamins that may reduce brain injury during a stroke and improve recovery.

## COMPLEMENTARY THERAPIES

### Acupuncture

Acupuncture, a form of traditional Chinese medicine, is postulated to regulate vital energy, called *qi*, via numerous techniques used to stimulate more than 2000 specified points on the body that are connected by meridians. The majority of clinical studies have focused on a form of acupuncture that uses metallic needles placed through the skin at various points, and are manipulated manually or by electrical stimulation, to unblock meridians and restore the balance of *qi*. Acupuncture is now widely practiced in the USA as a therapeutic intervention. In 1998 Harvard researchers published a national survey, which estimated that Americans made more than five million visits annually to acupuncture practitioners[1].

Many studies in animals and humans have demonstrated that acupuncture causes activation of multiple biological pathways, affecting various physiological systems in the

brain and peripheral nervous system[2]. Alterations in the secretions of neurotransmitters, neurohormones and other peptides as well as changes in blood pressure, flow and body temperature have been documented.[2]

There are numerous reports in the Chinese literature about the benefits of acupuncture in stroke rehabilitation[3]. These positive findings are largely due to the fact that the majority of stroke patients in China do not have access to conventional modalities of physical and occupational therapies. Acupuncture treatment in stroke patients has been found to reduce spasticity, improve motor function and alleviate post-stroke depression[4–6].

Recently, there have been various controlled clinical trials designed to assess the efficacy of acupuncture on motor recovery after stroke. One study conducted by Wong and co-workers randomized 128 patients within 2 weeks after stroke onset to receive either comprehensive rehabilitation plus electrical acupuncture ($n$=59) versus rehabilitation alone ($n$=59)[7]. Electrical acupuncture was administered five times per week on the hemiplegic side for a duration of 2 weeks. Stroke patients who received acupuncture in addition to conventional rehabilitation had significantly shorter hospital stays and improved functional outcomes compared to the control group upon discharge from the rehabilitation unit ($p$=0.03 and $p$=0.02, respectively).

Johansson and associates enrolled 150 patients with moderate to severe functional impairment, defined as a Barthel ADL Index of ≤70, in a multicenter, randomized, controlled trial. Acute stroke patients were randomized to receive one of three possible treatments, including acupuncture, transcutaneous electrical nerve stimulation (TENS) or sham electrostimulation (control group)[8]. Twenty treatments were performed over a 10-week period. After 12 months of follow-up, improvement in motor and activity of daily living functions were pronounced in all three treatment sets; however, there was no significant statistical difference observed between groups.

Sze and colleagues recently published a prospective, randomized, controlled trials from Hong Kong with similar results[9]. A total of 106 patients admitted for acute stroke rehabilitation were stratified to receive standard physical, occupational and speech therapies versus Chinese manual acupuncture in addition to conventional treatment modalities. After a 10-week treatment period, no statistically significant differences in outcome measures, including Fugl-Meyer assessment, Barthel Index and Functional Independence Measure, were observed between the two treatment arms.

Currently, faculty at the New England School of Acupuncture in collaboration with investigators from Harvard Medical School are undertaking a controlled study using functional magnetic resonance imaging (MRI) to evaluate alterations in brain activity and blood flow in participants, after real versus sham acupuncture, in an attempt to gain insight into the relationship between central biochemical changes and recovery.

Although many studies have been devised to investigate the potential efficacy of acupunc-ture on motor disability, results have been equivocal, owing to design limitations. While encouraging results have emerged showing possible benefit of acupuncture in stroke patients, controversy remains regarding the validity of this therapy when integrated into conventional post-stoke rehabilitation. Further investigation is warranted with welldefined protocols comprising sufficient power, appropriate control groups, standardized outcomes and statistical analysis to define the value of acupuncture

for patients disabled by stroke. In the meantime, it appears that a course of acupuncture treatment combined with conventional rehabilitation is reasonable in selected patients.

## Hyperbaric oxygen therapy

Hyperbaric oxygen therapy (HBOT) is emerging as a potential modality in the treatment of stroke patients. HBOT is administered via a specialized chamber, which compresses air to a pressure equivalent to 8–25 feet (2.5–7.5 m) feet below sea level. The air we normally breathe contains 21% oxygen, 78% nitrogen and 1% carbon dioxide. Under increased atmospheric pressure, patients inhale 100% oxygen, elevating arterial $O_2$ pressure to 2000 mmHg.

In focal cerebral ischemia, core tissue is surrounded by marginal areas of injured yet viable cells, which may be revived with adequate oxygenation[10]. Sustained tissue hypoxia impairs aerobic glycolysis, causing a cascade of ischemic neuronal damage resulting in apoptosis[10]. Increasing plasma oxygen concentration enhances oxygen diffusion at the cellular level, providing immediate oxygenation to poorly perfused tissue, maintaining cellular viability and promoting capillary angiogenesis[11]. In stroke patients, HBOT has been shown to reduce brain tissue swelling by constricting blood vessels without impairing tissue oxygen delivery[12].

Data in the literature regarding the efficacy of HBOT in reducing ischemic injury reveal variable outcomes in both human and animal studies[13–21]. These inconsistent results are probably due to small sample sizes, inadequate controls and differences in duration of exposure to HBOT.

Controlled, prospective analysis of HBOT exposure in stroke patients has been limited. Anderson and colleagues reported data from a controlled, double-blind protocol in which 39 patients with acute ischemic stroke were randomized to receive either 1 h HBOT at 1.5 atm, every 8h for a total of 15 exposures, versus sham (hyperbaric air) treatment[13]. The average elapsed time to treatment after onset of symptoms was 51.8 (range 10–148) h. The median number of completed treatments per patient was 9.4 secondary to protocol deviations. Statistical analysis of a graded neurological examination score was performed at baseline and after 4 months. The difference between treatment groups at 4 months was not significant, although patients in the sham group tended to have better outcomes. However, a retrospective review of baseline computerized tomography (CT) scans demonstrated that patients with larger infarcts were randomized to the HBOT group.

In 1995, Nighoghossian and colleagues published a double-blind study to assess the efficacy of HBOT on functional disability in patients with acute ischemic stroke. Thirtyfour patients with acute middle cerebral artery (MCA) occlusion were randomized within 24 h after onset to receive either HBOT, maintained at 1.5atm, or sham treatment[14]. Patients underwent ten consecutive daily treatments of 40 min duration. A functional assessment prior to therapy and at 6- and 12-month intervals was established using the Orgogozo, Rankin and Trouillas scales. The results showed a significant difference in reduced disability in the HBOT group after 1 year, according to the Orgogozo scale values ($p<0.2$). However, statistical analysis of the score difference between the pre and post-treatment groups was not significant ($p<0.16$).

Various animal models have demonstrated promising results when HBOT exposure occurs immediately after ischemic injury[15–21]. Sunami and co-workers examined the efffect of HBOT on infarct volume, cerebral blood flow, oxygen supply and lipid peroxidation in rats with acute cerebral ischemia[17]. HBOT was initiated in 19 adult rats, 10 min after ligation of the right middle cerebral and common carotid arteries. The treatment group was exposed to hyperbaric oxygen for a 2-hour duration. Comparisons with the control group demonstrated that rats treated with HBOT had a reduction in infarct volume by 18% and an increase in oxygen supply to the ischemic peripheral tissues by 20%. Additionally, cerebral blood flow and lipid peroxidation were not adversely affected by HBOT exposure.

Single-photon emission computerized tomography (SPECT) imaging plays an essential role in HBOT for patients with ischemic brain injury. A baseline scan followed by delayed imaging after HBOT intervention provides objective measurement of recoverable brain tissue. The presence of greater tracer uptake following HBOT exposure indicates perfusion enhancement or oxygeninduced reactivation of idling neuron metabolism[22]. SPECT in conjunction with MRI also permits assessment of the volume of ischemia. A larger degree of injury demonstrated by SPECT imaging when compared to MRI may represent the extent of salvageable tissue.

Quality centers offering HBOT follow protocols developed by Dr Richard A.Neubauer, one of the notable authorities in the expanding field[22]. After demonstration of viable tissue with SPECT imaging, 1.5 atm exposure is administered for 60 min once or twice daily up to a total of 40 treatments. After this series, the patient should have a repeat SPECT scan to evaluate the extent of progress. Therapy is continued in cycles of 40 exposures until the imaging has normalized or there is no further clinical improvement. If there is a clinical plateau while SPECT imaging suggests further areas of recoverable tissue, the pressure can be increased to 1.75 atm. Patients may require up to 200 HBOT exposures. The cost of treatment can range from $200 up to $1000 per hour, with a full course of therapy possibly extending to $40000. Currently, Medicare and insurance companies do not reimburse for HBOT treatment in acute or chronic stroke patients.

HBOT may be a reasonable adjunctive therapy in acute stroke based on a considerable amount of literature supporting the potential benefit of exposure in acute ischemic brain injury and its minimal adverse effects. Efficacy of HBOT in this population appears to be largely dependent upon the timing of the intervention; delaying treatment may exceed the necessary time window for oxygen to be beneficial. Further randomized, sufficiently powered, controlled investigations are warranted to determine the efficacy of hyperbaric oxygen in patients with both acute and chronic ischemic stroke.

## VITAMINS AND SUPPLEMENTS

Since much of the damage to the brain that occurs with a stroke appears to be caused by an increase in free radical generation, any of the hundreds of antioxidant supplements that are available could theoretically be beneficial. Some of these agents may also modify the release of various excitatory transmitters that also appear to promote stroke damage. However, in this review we restrict our discussion to agents that are commercially

available as supplements and that have at least been tested in experimental stroke model studies or preliminary clinical trials. An overview of these selected agents is given in Table 1.

### Citicoline

Cytidine-5-diphosphocholine (CDP-choline also called citicoline) is an essential precursor for the synthesis of phosphatidylcholine, a key component of cell membranes in the brain. Although citicoline is a naturally occurring endogenous compound, the sodium salt of citicoline is synthesized for clinical use. During ischemia, phosphatidylcholine is broken down into free fatty acids which in turn are used to generate free radicals, which potentiate ischemic injury[23]. The exogenous administration of CDP-choline has been shown in animal models to reduce this cell-membrane breakdown, leading to increased synthesis of phosphatidylcholine and decreased levels of free fatty acids[24,25].

**Table 1** Supplements for potential stroke recovery

| *Supplement* | *Beneficial in animal stroke trials* | *Beneficial in clinical stroke studies* | *Significant side-effects* | *Suggested oral dose* |
|---|---|---|---|---|
| Citicoline | yes | yes | no | 1000 mg bid |
| *Ginkgo biloba* | yes | equivocal | yes* | 120 mg bid |
| α-Lipoic acid | yes | no | no | 300–1200 mg/day |
| Inosine | yes | no | yes† | 2–3 g/day |
| Vitamin E | ‡ | no | yes** | 400 IU qd |
| Melatonin | yes | no | yes†† | 1–5 mg po hs |
| $Mg^{2+}$ | yes‡‡ | yes‡‡ | yes*** | 800 mg po qd |

bid, twice a day; IU, international units; qd, once a day; po, by mouth; hs, at bedtime *Increased risk of bleeding in the brain; †increased risk of gout; ‡only when combined with α-lipoic acid; **may increase risk of bleeding in the brain; ††may worsen autoimmune disease; ‡‡intravenous administration only; ***gastrointestinal symptoms

The use of citicoline treatment has been shown to be beneficial in several animal models of ischemia or hypoxia[26,27], including recent studies with reversible focal occlusion[28] and an intracerebral hemorrhage model[29]. These studies have found that citicoline treatment decreases free fatty acid concentration, improves neurological signs, decreases neurological deficits and improves neuronal survival.

Citicoline has previously been shown to improve neurological and global function in several randomized clinical stroke treatment trials outside the USA[30–32], with initial treatment started up to 14 days after stroke. Citicoline was studied in three placebo-controlled trials sponsored by Interneuron Pharmaceuticals in the USA involving a total of 1560 patients with medium to large strokes[33–35]. The citicoline was started within 24 h

of stroke onset and was given orally for 6 weeks, with the optimal dose appearing to be 1000mg orally twice a day. In these trials, citicoline appeared to be safe with essentially no side-effects. Overall, a modest (~20%) improvement in both neurological and functional recovery at 3 months was found, compared to placebo, on several traditional stroke outcome measures. Unfortunately, the company instead chose to use a novel neurological measure as the primary outcome variable which did not detect this benefit, therefore the Food and Drug Administration (FDA) did not view the results as positive. A further study is planned using traditional endpoints for 2004. In the meantime, citicoline is available as CDP-choline at various Internet supplement stores. A dose of 1000 mg twice a day is recommended for 6–12 weeks. This would cost approximately $80 per month. Although the American trials started therapy within 24 h, the favorable results of the study by Tazaki and co-workers[32] suggest a possible benefit even when treatment is started up to 2 weeks after the stroke. Since citicoline may also improve memory, owing to its effects on acetylcholine, it may especially be useful in patients who have memory dysfunction following their stroke. There do not appear to be any significant side-effects or other drug interactions.

### *Ginkgo biloba*

*Ginkgo biloba* extract is extracted from the leaves and nuts of the *Ginkgo biloba* tree and has been used for centuries in Asia and Europe for a variety of disorders[36]. It has recently been recognized in the USA after showing benefit in clinical studies of memory disorders[36,37]. Some of the mediators of stroke injury appear to be due to an inflammatory response involving free radical generation, activated leukocytes, and platelet activating factor (PAF)[38]. The extract contains flavonoids which appear to possess strong free radical scavenging and anti-inflammatory properties[39], and terpenoids (ginkgolides A and B)[40], which inhibit PAF and decrease free radical release[41]. Treatment with *Ginkgo biloba* extract has shown beneficial effects in reducing reperfusion injury in central nervous system (CNS) global ischemia and trauma experimental models[42].

We recently investigated the neuroprotective efficacy of *Ginkgo biloba* extract in the treatment of CNS ischemic injury using an animal model that closely approximates clinical stroke[43]. Sixty mice were randomized to treatment with the extract given orally for 7 days: low dose, 50mg/kg per day; high dose 100mg/kg per day; or matched placebo. On day 7, reversible middle cerebral artery occlusion was produced by advancing a siliconecoated 8–0 filament into the internal carotid artery for 45 min followed by reperfusion. At 24 h, the animals were rated on a clinical scale and the stroke volume was determined. Infarct volume at 24 h (mean±SD): low dose, 13±5 $mm^3$; high dose, 22±12 $mm^3$; and placebo ($n$=20), 20±10$mm^3$ ($p$=0.03 overall; $p$=0.02 low dose vs. placebo). Ten per cent of the high-dose group showed significant intracerebral hemorrhage (ICH) within the stroke while no ICH was seen in the other groups. This study found that oral *Ginkgo biloba* produced significant reductions in stroke infarct volume. However, this beneficial effect appeared to be dose related, with higher doses potentially increasing the risk of ICH. One clinical case report described bilateral hematoma formation, presumably due to the *Ginkgo biloba* extract[44]. Clinically, the extract is readily available and widely used for the treatment of memory disorders. Several trials have found small but significant beneficial effects (120–240 mg/day) on memory and social function in early

dementia[45–47]. *Ginkgo biloba* extract is currently being studied at the Kessler Institute for Rehabilitation in clinical stroke recovery. Patients who are at least a month post-stroke receive either 240 mg of the extract or placebo per day. No results are yet available.

Given the encouraging experimental results, *Ginkgo biloba* extract should be considered in selected patients following a stroke, particularly in patients with memory difficulties. A dose of 60–120 mg twice a day is suggested, taken for at least a month. However, given the bleeding risk of *Ginkgo biloba* extract, we feel it should not be used in patients who are on coumadin or in any patients with a history of brain hemorrhage.

### α-Lipoic acid

α-Lipoic acid is a thiol antioxidant (similar to glutathione) that is absorbed from the diet and crosses the blood-brain barrier[48]. The mechanism of action appears to be due to its ability to substitute for glutathione (GSH). Four antioxidant properties have been demonstrated: it has metal chelating capacity; it can scavenge reactive oxygen species (ROS); it can regenerate endogenous antioxidants including vitamins E and C; and it can repair oxidative damage[49]. α-Lipoic acid has been shown to be neuroprotective in several studies involving permanent focal CNS ischemia. Wolz and Krieglstein[50] studied α-lipoic acid in permanent focal MCA models in both rats and mice and found that a dose of 100 mg/kg of α-lipoic acid given 2 h prior to ischemia reduced infarct volume at 48 h. Using the same permanent MCA occlusion model, Prehn and associates found that a dose of 50 mg/kg of α-lipoic acid given subcutaneously 30 min prior to ischemia produced significant infarct reduction in rats and mice[51].

We have studied α-lipoic acid in the mouse MCA reperfusion (reversible) model.[43] Treatment with α-lipoic acid produced a significant reduction in lesion size at 24 h: 100mg/kg LA ($n$=12) produced 16.8±8.3mm$^3$; placebo ($n$=12) produced 27.2±14.6 mm$^3$($p$<0.05; df=21; $t$ value 2.08). α-Lipoic acid also produced a significant improvement in neurological function at 24 h: α-lipoic acid 9.5±1.2; placebo 11.2±1.8 ($p$=0.02; df=21; $t$ value 2.49). There was no evidence of ICH or sideeffects in any of the animals.

There are no reports of the use of α-lipoic acid in clinical stroke. Although the optimal clinical dose in stroke is not known, a dose of 300–1200 mg orally per day is currently being studied in other neurological diseases. No significant side-effects or drug interactions have been reported at these doses to date.

### Inosine

Inosine is a nucleoside (a building block for DNA and RNA) found naturally in muscle tissue as a precursor to adenosine. It is available as a supplement and is used by some athletes to improve performance (unproven). In a recent study, adult rats with a stroke were treated with inosine given via intrathecal pumps directly into the brain[52]. Compared to placebo, treated animals showed a 50% improvement in leg function at 4 weeks. In addition, the investigators found that the treated animals had an increase in axon growth from the undamaged hemisphere crossing over to the stroke area. They are currently starting initial clinical trials using intrathecal administration of inosine. Unfortunately, inosine given orally is converted to uric acid and little, if any, inosine reaches the brain. However, since uric acid itself is a very powerful antioxidant, inosine is being used at

doses of 3000 mg orally in multiple sclerosis patients to increase their uric acid levels in the brain. Oral inosine might therefore also be beneficial in stroke. However, this has not yet been investigated. Although inosine does appear to have an exciting potential in stroke recovery, the only administration method studied to date is directly into the brain. If one chooses to use oral inosine for the possible beneficial effects via uric acid, a total dose of 2–3000 mg/day, administered as three smaller doses during each day, is suggested. Uric acid levels should be followed to keep at 8–9 mg/dl, to avoid gout.

## Vitamin E

Vitamin E or α-tocopherol is an antioxidant with additional mild antiplatelet effects. There have been limited studies investigating the role of vitamin E in stroke recovery. Several animal trials have found that animals deficient in vitamin E have larger strokes[53]. However, the value of additional supplementation has not been demonstrated. Although not effective on its own, recent experimental studies have found that vitamin E may have a synergistic effect in reducing stroke injury when combined with α-lipoic acid[54]. The only reported clinical study was a very small (60 patient) trial that found that patients supplemented with vitamin E (300 mg/day orally) had improved neurological function compared to controls at 6 weeks[55]. Vitamin E and other antioxidants have been extensively studied in stroke prevention trials. There is no evidence that vitamin E, vitamin C, or β-carotene supplementation reduces the risk of recurrent stroke[56]. In fact, vitamin E supplementation appears to increase the risk of the hemorrhage type of stroke[57]. This hemorrhage effect may be due to the antiplatelet actions of α-tocopherol[58]. Overall, it appears that for vitamin E to have a benefit it must be given prior to the stroke, apparently in conjunction with lipoic acid. Although it may be considered in selected patients at high risk for stroke, for example prior to carotid endarterectomy, the routine supplementation of vitamin E after stroke is not supported.

## Melatonin

Melatonin, a metabolite of tryptophan, is a hormone produced naturally in the pineal gland. It is important in regulating sleep, and may play a role in maintaining circadian rhythm, the body's natural time clock. It is widely used as a supplement to induce sleep and help with jet lag. Melatonin also is a potent scavenger of free radicals and an indirect antioxidant, and has been shown to protect against free radical injury in the brain[59]. It has been found to be effective in several experimental stroke studies. Kondoh and colleagues found that 6 mg/kg orally given just prior to MCA occlusion in rats reduced the volume of cerebral edema on MRI at 24 h by 43%[60]. In a similar study, Pei and co-workers found that either 5 or 15 mg/kg of melatonin given intraperitoneally just prior to MCA occlusion in rats produced a significant reduction in infarct volume at 3 days[61]. Finally, Sinha and associates found that both 20 and 40mg/kg of intraperitoneal melatonin given at the onset of ischemia reduced infarct volume and improved neurological function in the rat in brain free radicals and increased GSH[62]. MCA model. This study also found a reduction Interestingly, animals that have had their pineal glands removed (no melatonin) had much larger infarcts[63]. All of these studies administered melatonin just prior to ischemia, so it is not known whether it would still be effective if given after the stroke.

No clinical experience with melatonin treatment in acute stroke patients has been reported.

Based on the above strong preclinical data, it appears that the short-term use of melatonin for acute stroke patients is reasonable. The exact clinical dose is not known, as animal dosages are not equivalent to human dosages. Doses of 1–5 mg orally at night are safely used for sleep. A sustained-release version is available. It should not be used in patients with autoimmune disease (it may increase the immune response) or in patients on antidepressants (serotonin or monoamine oxidase inhibitors).

### Magnesium

Supplementation with the cationic mineral magnesium is widely used by naturopaths for a variety of conditions ranging from high blood pressure to insomnia. Since it inhibits excessive neuronal transmission, it may be especially useful in neurological conditions involving muscle twitching, cramping, or spasticity and even seizures. It has been widely studied as a potential stroke therapy. Magnesium is involved in multiple physiological processes that may be relevant to cerebral ischemia, including antagonism of glutamate release, NMDA receptor blockade, calcium channel antagonism and maintenance of cerebral blood flow. In animal models, magnesium sulfate given intravenously consistently reduces cerebral infarct volume after MCA occlusion, with evidence of a dose-response effect and with benefit seen up to 6 h after stroke[64]. Five small clinical trials totaling 206 patients have been reported. These trials found a significant reduction in death or dependence at 30 days and improved neurological function[65]. However, owing to the small number of patients, these results are far from conclusive. These trials administered magnesium as an intravenous loading infusion, usually over 15 min, within a few hours of the stroke followed by a maintenance infusion over 24 h or longer. Based on these results, a large multicenter study involving over 130 centers worldwide is in progress. This Intravenous Magnesium Efficacy in Stroke (IMAGES) trial has now recruited over 2200 participants within 12 h of stroke onset, with results expected in 2003.

Although the potential for magnesium as a stroke therapy appears promising, all of these studies used intravenous administration. Owing to poor oral absorption, it would be difficult to achieve the same plasma magnesium levels with oral supplementation. In addition, it appears that, unlike the mechanisms of antioxidants or citicoline, the benefits of magnesium involve a reduction in excessive excitatory transmitters after stroke, which occurs only in the first few hours. Taking magnesium after this is unlikely to improve recovery. Therefore, we do not recommend oral supplementation for stroke recovery at this time. If oral magnesium is used for stroke-related conditions (e.g. spasticity, muscle pain, high blood pressure) doses up to 800 mg/day should be used with amino acid complexes (e.g. magnesium glycinate) producing fewer side-effects than the less expensive magnesium oxide.

### Miscellaneous vitamins and antioxidants

Vitamin C and β-carotene have not been found to be beneficial in stroke following oral administration, probably owing to their poor ability to cross the blood-brain barrier. Also,

although coenzyme Q10 reduces cardiac injury and is widely used as a therapy in congestive heart failure, its value as a potential stroke therapy has not yet been investigated.

In this review we have focused on agents or modalities that may improve stroke recovery. The best 'treatment' for stroke is preventing one in the first place. There are a variety of complementary therapies, including diet and exercise, that have been shown to reduce the risk of recurrent stroke. In fact, several supplements that improve cholesterol values including fish oil and niacin are now widely used by physicians practicing conventional medicine. Several recent studies also suggest that supplementation with the B vitamin folic acid (1 mg/ day) reduces both cardiovascular and stroke risks through its action on homocysteine[66]. A full review of these stroke prevention strategies would require a chapter on its own.

## SUMMARY

A variety of complementary therapies appear to have potential benefit in stroke recovery. Acupuncture is widely used and appears to be as beneficial as conventional rehabilitation modalities. It may be of particular use in patients who also have pain. The benefits of hyperbaric therapy are less clear and the cost of this procedure argues against its use in most patients. Although definitive clinical studies have not been carried out, many antioxidant supplements appear to have potential efficacy in stroke recovery. One of these, CDP choline, has been extensively studied and should be considered in selected patients.

## ACKNOWLEDGEMENTS

The authors would like to thank Anne Tillinghast for her expert assistance in the preparation of this manuscript.

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# 17
# Multiple sclerosis

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*Complementary Therapies in Neurology: An Evidence-Based Approach*
Edited by Barry S.Oken
ISBN 1-84214-200-3 

## PATHOGENESIS AND CONVENTIONAL TREATMENT OF MULTIPLE SCLEROSIS

Multiple sclerosis (MS) is the most common disabling neurological disease of young and middle-aged adults in North America and Europe[1]. Pathologically, MS consists of multifocal areas of demyelination, referred to as 'plaques', in the brain, spinal cord and optic nerves. In these areas there is destruction of the myelin sheath around axons with relative sparing of axons, although axon damage also occurs in MS. Inflammatory cells (macrophages and lymphocytes) are present when there is active demyelination within MS plaques, indicating that MS is an inflammatory disease. Magnetic resonance imaging (MRI) provides a means of visualizing MS lesions within the brain and spinal cord. Clinically, MS can cause a variety of neurological problems depending on the location and severity of MS plaques. In about 85% of cases, MS starts with a relapsing-remitting course[2]. Patients experience relapses or attacks of MS during which they develop a new neurological problem, return of an old problem that had resolved or worsening of pre-existent symptoms. Relapses develop over a few days or weeks and then a period of improvement and stability ensues. Patients average about one clinical relapse every 2 years. In between relapses, patients are clinically stable, although they may have a variety of permanent neurological symptoms resulting from previous tissue injury. However, relapses that cause symptoms represent only the 'tip of the iceberg' of disease activity in this stage of the illness. Serial MRI studies in MS patients have disclosed that asymptomatic new MS lesions appear within the brain 5–10 times more commonly than symptomatic lesions, and these asymptomatic 'relapses' cause permanent damage that contributes to overall MS disease burden[3]. About 50% of patients with relapsing-remitting MS will enter a progressive phase of the disease 5–15 years after onset. Steady worsening characterizes this phase of the illness, called secondary progressive MS. Patients with secondary progressive MS may or may not continue to have relapses. About 15% of MS patients have progressive worsening from the onset of their illness, a form of MS referred to as primary progressive MS. While MS is rarely fatal, it is usually disabling, with about one out of three patients losing the ability to walk 15–20 years after onset.

While its cause remains uncertain, MS is believed to be an immune-mediated disease induced in genetically susceptible individuals by one or more environmental exposures[1].

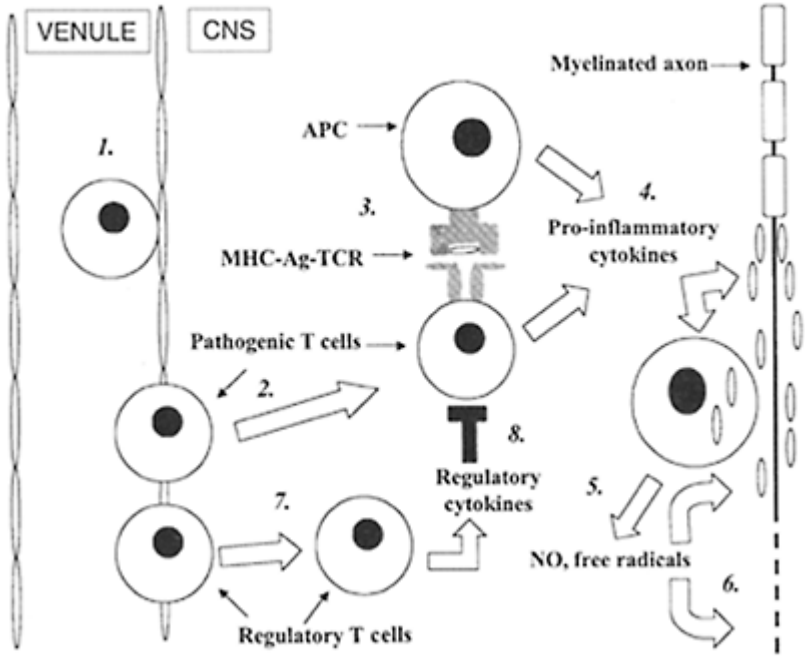


**Figure 1** Model of acute multiple sclerosis plaque. Activated T cells enter the central nervous system (CNS) by adhering to endothelial cells in venules *(1)* and then passing through the blood-brain barrier *(2)*. Pathogenic CD4+ T cells then recognize antigens within the CNS, which may be fragments of myelin proteins or viral antigens expressed as part of a latent infection *(3)*. Recognition of antigen involves binding of the T-cell receptor (TCR) to a major histocompatibility complex (MHC) class II molecule that contains a peptide antigen (Ag) on the surface of an antigen-presenting cell (APC), such as a microglial cell,

macrophage or astrocyte. The activated T cells and APCs then release pro-inflammatory cytokines, including lymphotoxin, tumor necrosis factor-α and interferon-γ, which directly injure myelin and activate macrophages *(4)*. Activated macrophages release cytokines, nitric oxide (NO), free radicals and proteases that injure myelin and axons *(5, 6)*. Regulatory T cells enter the CNS (7) and release regulatory cytokines *(8)*, such as transforming growth factor-β and interleukin-10, that down-regulate pathogenic T cells, 'turning-off' the acute inflammatory response

Inflammatory cells mediate the destruction of myelin and axons in acute MS plaques (Figure 1). The inflammatory cells involved in MS include T lymphocytes, macrophages and plasma cells. It is believed that a subset of T lymphocytes initiates the acute MS lesions, recognizes one or more antigens within the central nervous system (CNS), becomes activated, and then initiates an inflammatory cascade that results in demyelination and axonal injury. The targets of this T-cell-mediated inflammation are uncertain but may be myelin antigens or perhaps antigens expressed as part of a latent viral or atypical bacterial infection. The mediators of tissue damage include macrophages, which cause damage by releasing soluble inflammatory substances, such as cytokines and free radicals, or by actively stripping myelin from the axon sheath. Activated T cells can also release pro-inflammatory cytokines that can contribute to tissue damage. Finally, anti-myelin antibodies can damage myelin either by initiating complement-mediated demyelination or facilitating macrophage phagocytosis of myelin. The disease process is halted by apoptosis of the disease-initiating T cells and recruitment of regulatory T cells into the CNS.

Conventional medicine treatments for MS are divided into two broad categories: those that alter the disease course and those that help manage symptoms. Diseased-modifying therapies include the use of corticosteroids to shorten the duration of MS relapses, and antiinflammatory therapies, such as recombinant interferon-β (IFN-β), glatiramer acetate and immunosuppressants, to decrease disease activity in patients with relapsing MS. Symptomatic therapies encompass a variety of medications and physical modalities to manage specific symptoms. These include the use of stretching exercises and baclofen to treat spasticity or anti-cholinergic medications or intermittent self-catheterization to manage a neurogenic bladder.

## COMPLEMENTARY AND ALTERNATIVE THERAPIES IN MULTIPLE SCLEROSIS

A number of surveys have indicated that MS patients in the USA commonly use complementary and alternative medicine (CAM) therapies. In these published surveys, 55–67% of respondents had tried CAM treatments[4–7]. In an unpublished survey of 5200 members of the Oregon Chapter of the National MS Society, 96% of the 1913 respondents had tried at least one CAM therapy and 88% were currently using CAM. In the Oregon survey, the CAM therapies most commonly used were a low-fat diet (67% of respondents), essential fatty acid supplementation (45%), yoga (23%), meditation (16%) and herbal supplements (46%). Physicians sometimes believe that MS patients try CAM therapies out of desperation or in place of conventional therapies. However, patients at all levels of disability reported using CAM therapies equally, suggesting that CAM use is not restricted to highly disabled individuals who have 'nothing to lose'. In addition, most MS patients who use CAM therapies do so in addition to conventional therapies. Berkman and colleagues found that 53% of respondents used a combination of CAM and conventional therapies and only 6% reported using CAM treatments exclusively for their MS[4]. At least in the USA, over 50% of MS patients report trying CAM therapies and generally do so in combination with conventional therapies.

MS patients who use CAM treatments typically report that they derive some benefit from the use of CAM. Berkman and co-workers found that 91% of respondents who indicated that they used CAM therapies reported deriving benefit from the therapies[4]. Most patients indicated that the CAM treatments improved their quality of life and helped with a variety of MS symptoms, such as fatigue or spasticity. Only 12% felt that the CAM therapies had favorably altered the course of their MS and 9% indicated that they had experienced some side-effects from one or more CAM therapies. In the Oregon survey, over 50% of respondents rated at least one CAM therapy that they had tried as being 'very beneficial'. This survey also indicated that MS patients perceived a wide range of benefit for various CAM therapies. The fraction of patients rating 18 specific CAM therapies as being 'very beneficial' ranged from 13 to 60%, with the therapies receiving the highest ratings being a low-fat diet (60% of users rating it as 'very beneficial'), yoga (52%) and meditation (46%). These data suggest that patients perceive varying benefit from different therapies. MS patients who use CAM report improvement in quality of life and symptom management and also discern differential benefit among the various CAM treatments.

Despite the common use of various CAM therapies by MS patients, there is a paucity of well-designed clinical trials assessing CAM treatments for their ability to modify the disease course or manage specific symptoms.

### Diet therapy

Many MS patients follow low-fat diets. Among the respondents to the Oregon CAM survey, 67% indicated that they had tried some form of low-fat diet, including 27% who had followed the Swank diet; 36% were still on a low-fat diet at the time of the survey. Dr Roy Swank popularized the use of a low-fat diet as a treatment for MS through his book, which is now in its third edition[8]. The Swank diet consists of a diet that is very low

in saturated fats (no more than 15–20 g/day) supplemented with cod liver oil[8]. Swank began treating patients with his low-fat diet in 1948 because of epidemiological studies indicating that MS was more common among populations who consumed a diet high in saturated fats compared with those that had a diet that was low in fat or contained substantial quantities of fish (reviewed in references 9 and 10). Swank never performed a randomized, controlled trial of the diet. However, a longterm follow-up (mean duration of 25 years) on his original cohort of patients who started the diet suggested that the MS patients who adhered to his diet had a lower death rate and were less disabled than those who had stopped following the diet[11,12].

A recent study evaluated the effects of a diet low in saturated fats combined with fish oil supplementation and vitamin B-complex and vitamin C in 16 patients with early relapsing-remitting MS[13]. All patients were placed on the low-fat diet with supplements, and diet adherence was monitored over 2 years by 4-day dietary record and plasma fatty acid levels. The dietary record indicated that after 2 years there was a significant increase in fish intake and a reduction of food items containing saturated fats. In addition, there was a significant increase in plasma levels of ω-3 fatty acids and a significant decrease in plasma ω-6 fatty acids. Over the 2 years of the study, patients had a significant reduction in both relapse rates and disability compared with their condition prior to entering the study. However, this was not a randomized trial and there was no comparison group, although the results are consistent with those of Swank's long-term observational study. Additional support for the benefit of a low-fat diet comes from a case-control study in Canada that found a positive association between animal product intake and the risk of developing MS and an apparent protective effect from diets enriched in fruits, vegetables and grains[14].

The Swank diet is enriched in ω-3 fatty acids and, as reviewed below, ω-3 fatty acids appear to have anti-inflammatory effects. The Swank diet advocates fish as a major source of protein and fish, particularly cold-water fish, are rich in the ω-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). In addition, the Swank diet uses cod liver oil, a source of ω-3 fatty acids, as a supplement. The Swank diet and other low-fat diets enriched in ω-3 fatty acids may have anti-inflammatory effects, providing a theoretical rationale for their benefit in treating MS. Unfortunately, a well-designed study has never been conducted to determine the effectiveness of a low-fat diet in treating MS.

## Essential fatty acid supplementation

The essential fatty acids (EFA) are divided into two major groups, the ω-3 fatty acids and the ω-6 fatty acids.

### *Omega-3 fatty acids*

There is a rationale for supplementation with EPA and DHA in the treatment of MS. As already reviewed, MS is an acquired immunemediated disease mediated by T cells, macrophages, anti-myelin antibodies and pro-inflammatory cytokines. A variety of studies have indicated that ω-3 fatty acids have anti-inflammatory effects. *In vitro,* animal and *ex vivo* human studies have reported a decrease in mRNA and protein levels of a

number of cytokines and other molecules that are implicated in the immunopathogenesis of MS, including tumor necrosis factor-α (TNF-α), interferon-pγ (IFN-γ), interleukin (IL)-1, IL-2 and adhesion molecules[15–19]. One study demonstrated that fish oil supplementation, which is enriched with EPA and DHA, decreased proinflammatory cytokine secretion in MS[20]. In this study, production of IL-1β, TNF-α, IL-2 and IFN-γ in unstimulated and stimulated peripheral blood mononuclear cells (PBMC) from patients with MS was evaluated. Twenty subjects with MS were supplemented with 6 g/ day of fish oil containing 3.0 g EPA and 1.8 g DHA for 6 months. After 3 and 6 months of fish oil supplementation there was a significant decrease in the production of IL-1β, TNF-α, IL-2 and IFN-γ by PBMC. Cytokine levels returned to baseline values after a 3-month wash-out period. This study suggested that fish oil supplementation can decrease pro-inflammatory cytokines postulated to be important to the pathogenesis of MS.

How ω-3 fatty acids influence inflammatory processes is not entirely understood[19,21]. Omega-3 fatty acid supplementation alters the type of eicosanoids, such as leukotrienes and prostaglandins, that inflammatory cells produce and thereby influence inflammatory responses. Omega-3 fatty acids may also inhibit up-regulation of a key pro-inflammatory transcription factor, nuclear factor-κB, which regulates expression of a variety of molecules, such as TNF-α, matrix metalloproteinases and some adhesion molecules, involved in MS. These effects provide a rationale for considering the use of ω-3 fatty acid supplementation as an adjuvant therapy in MS.

There has been only one randomized controlled trial of ω-3 fatty acid supplementation in MS[22]. This was a large ($n$=312) doubleblind placebo-controlled trial in which MS patients were randomized to receive either 20 capsules of fish oil per day or olive oil containing 72% oleic acid for 2 years. In the fish oil supplementation group, the total daily dose of EPA and DHA was 1.71 g and 1.41 g, respectively. Outcome measures included changes in disability, relapse rate and severity of relapses. At the conclusion of the study there was a trend favoring fish oil supplementation for all outcome measures, although none achieved statistical significance. For instance, 43% of the fish oil group had worsened on the Kurtzke Disability Status Scale compared with 52% of the placebo group ($p$=0.07). While the results did not achieve statistical significance favoring ω-3 fatty acid supplementation, the study was not optimally designed. Both groups in the study were advised to follow a diet low in animal fat, and had comparable changes in serum fatty acid content over the course of the study. The dietary changes in the control group thus may have biased the study against detecting an effect of the ω-3 fatty acid supplementation.

Because of the anti-inflammatory effects of ω-3 fatty acids, additional research appears warranted on the therapeutic benefits of ω-3 fatty acid supplementation in MS.

### *Omega-6 fatty acids*

The scientific rationale for ω-6 fatty acid supplementation in MS is less well substantiated than for ω-3 fatty acid supplementation. Supplementation of ω-6 fatty acids significantly increased the production of transforming growth factor (TGF) β-1 in the PBMC of healthy subjects[23] and TGF-β1 is an antiinflammatory cytokine that might be beneficial in MS[24]. Two studies in an animal model of MS reported that supplementation with linoleic acid, which is rich in ω-6 atty acids, decreased the severity of disease[25] and

reduced inflammation in the CNS[26]. There is thus some experimental basis for considering ω-6 fatty acid supplementation in MS.

Linoleic acid supplementation for the treatment of MS has been investigated in three double-blind placebo-controlled clinical trials using olive oil as the placebo[27–29]. Although the results of the studies were mixed (two showed a positive effect and one did not), a meta-analysis of the three studies suggested that patients supplemented with linoleic acid had a smaller increase in disability and fewer severe relapses compared with patients supplemented with olive oil[30]. These studies used a sunflower seed oil emulsion at a sufficient dosage to provide a daily supplementation of I7.2g of linoleic acid. Unlike the trial using fish oil supplementation, subjects in these studies were not advised to alter their diets.

Evening primrose oil, which is enriched in the ω-6 fatty acid γ-linolenic acid, is commonly used by MS patients. It has been suggested that γ-linolenic acid might be more effective than linoleic acid, owing to its easier incorporation into brain lipids and its possibly greater effect on immune function[31]. However, evening primrose oil contains low levels of γ-linolenic acid and the product is relatively expensive. Large and prohibitively expensive amounts of evening primrose oil would need to be used to obtain adequate supplementation. In addition, a single pilot trial of evening primrose oil in MS failed to demonstrate any clinical benefit[27]. Based on these considerations, evening primrose oil appears to be of no use in treating MS.

In summary, there is evidence from clinical trials that supplementation with the ω-6 fatty acid linoleic acid may have a modest benefit in the treatment of MS. It is worth noting that ω-6 fatty acid supplementation is probably not useful for individuals following a low-fat diet, which is typically enriched in ω-6 fatty acids.

## Exercise

Several studies have demonstrated that most MS patients are deconditioned and that a regular exercise program can improve conditioning and improve fatigue and quality of life measures[32–38]. Four studies reported that, compared to an MS non-exercising group, the MS exercising group demonstrated an improvement in subjects' reports of fatigue, quality of life, and well-being[32,33,37,38]. Two forms of CAM exercise have been evaluated in MS: t'ai chi and yoga. There have been two reported pilot studies evaluating the use of t'ai chi in people with MS[34,36]. To evaluate the effects of training in the principles of 'mindful-ness of movement' from t'ai chi in MS, 16 patients with secondary progressive MS were divided into eight matched pairs and each pair was randomized into a 'mindfulness' group or a'usual care' group. Although there was no difference between groups in measures of balance, there was a significant improvement in the 'mindfulness' group in self-reported measures of MS-related symptoms[36]. In a non-randomized uncontrolled pilot study, 19 patients with MS underwent an 8-week training course in t'ai chi. Outcome measures compared pretraining to post-training scores. Post-training outcomes demonstrated an improvement in walking speed, hamstring flexibility and selfreports of well-being and quality of life[34].

Yoga is another commonly used form of exercise among people with MS and many chapters of the National MS Society sponsor yoga programs for their clients. A trial that randomized 69 MS patients to yoga, exercise on a stationary bicycle or a 'wait-list' group

demonstrated improvement in quality of life measures for both exercise groups compared with the 'wait-list' group, but no significant differences between the yoga and conventional exercise groups[39].

These studies demonstrate the feasibility of MS patients participating in t'ai chi and yoga exercise programs, particularly if they are modified for the level of disability of the participants. There is no evidence at present to suggest that CAM approaches to exercise are superior to conventional forms of exercise, such as swimming or use of a stationary bicycle.

### Stress reduction

Many MS patients report that stress worsens their MS symptoms and precedes either the onset of their MS or relapses. In a review of the research literature assessing associations between psychological stress and worsening of MS symptoms, an expert panel concluded that there was a possible relationship between antecedent emotional stress and either MS onset or relapses[40]. A prospective longitudinal study of MS patients designed to examine the relationship between stressful life events, psychological stress and disease activity as measured by MRI, found that increased conflicts and disruptions in routine were associated with an increased risk of developing new brain lesions[41]. The authors concluded that, while they had identified a relationship between antecedent stressors and disease activity, this relationship was not sufficiently robust to predict clinical exacerbations reliably in individual patients. In a subsequent study on the same subjects the relationship between coping skills, stress and the development of new brain lesions as measured by MRI was examined[42]. This study reported that greater use of distraction was found to be a significant modifier of the relationship between stress and new lesions. Emotional preoccupation was marginally associated with an increased relationship between stress and new lesions. The authors concluded that these find-ings provide modest support for the hypothesis that coping can moderate the relationship between stress and MS disease activity.

There are a number of CAM approaches advocated for stress management including yoga, t'ai chi, prayer, meditation and massage therapy. A number of studies have demonstrated the ability of meditation to lower stress and improve symptoms in patients with chronic illnesses, such as rheumatic disease[43], irritable bowel disease[44] and cancer[45,46]. In addition to the psychological benefits of meditation, experienced meditators have been reported to have enhanced biochemical and physiological functioning when compared to non-meditators[47–49]. Studies on the use of t'ai chi and yoga as forms of exercise for MS patients did not specifically assess effects on stress management. Whether various CAM approaches to stress management might be useful for patients with MS is presently unknown.

### Antioxidants

As discussed above, free radicals may play an important role in tissue injury in MS, providing a rationale for the use of antioxidant supplements in the treatment of MS.

### *Selenium*

Several studies have demonstrated a reduction in glutathione peroxidase activity in the erythrocytes and leukocytes of patients with MS[50–53]. One small study found a significant positive association between an impaired glutathione S-transferase genotype and increased numbers of active lesions in MS patients[54]. Selenium is a component of a wide range of selenoproteins, glutathione peroxidases being a major class of selenoproteins. Release of selenoproteins is part of the innate cellular responses to oxidative stress[55]. In a macrophage cell line, selenium deficiency resulted in an increase in both gene and protein expression of both inducible nitric oxide synthase (iNOS) and nitric oxide (NO) levels in lipopolysaccharide-stimulated cells[56]. There is only one published study assessing the effects of selenium supplementation in MS. This study reported that supplementation of 18 MS patients with 6 mg/ day of sodium selenite, 2 g/day of vitamin C and 480mg/day of vitamin E for 5weeks increased glutathione peroxidase five-fold[57]. Unfortunately, clinical parameters were not evaluated. There are no randomized controlled trials assessing the clinical benefit of selenium supplementation in MS.

### *Vitamins C and E*

There have been no therapeutic trials evaluating the clinical effects of vitamin C and vitamin E supplementation alone in MS. Both vitamins can decrease lipid peroxidation and might therefore be beneficial in limiting tissue injury in MS. Isoprostane levels, a measure of lipid peroxidation, are increased in a number of neurological disorders, including MS, Alzheimer's disease, Huntington's disease, and Creutzfeldt-Jakob disease[58]. One study reported a significant increase in isoprostane levels in the cerebrospinal fluid (CSF) of MS patients compared to subjects with other neurological diseases[59]. The effects of vitamin C and E supplementation on lipid peroxidation in a variety of populations, including healthy subjects, congestive heart failure patients, smokers, non-smokers and hypercholesterolemic patients[60–65], have been assessed, and the majority of these studies have reported a decrease in isoprostane level from supplementation of either of the vitamins[60–62,65]. Whether supplementation with vitamins C and E would provide any benefit in MS is unknown.

### *α-Lipoic acid*

α-Lipoic acid (ALA) and its reduced form, dihydrolipoic acid (DHLA), are potent antioxidants with multiple modes of action. ALA/ DHLA can regenerate other antioxidants, such as glutathione, vitamin C and vitamin E, serve as a reactive oxygen species scavenger, repair oxidative damage and chelate metallic ions involved in oxidative injury. ALA is absorbed from the diet and synthesized *de novo*, is readily converted intracellularly to DHLA, and crosses the blood-brain barrier; both ALA and DHLA are present in both extracellular and intracellular environments[66]. Although there are no reports on the effectiveness of ALA in MS patients, one study in an animal model of MS demonstrated a significant benefit for ALA. ALA given subcutaneously at a dose of 100 mg/ kg per day completely suppressed disease and did so by preventing T-cell

trafficking into the spinal cord[67]. The antioxidant properties of ALA and the therapeutic benefits of ALA in an animal model of MS suggest that it may warrant investigation as a treatment for MS. It is also worth noting that ALA has been shown in several trials to be beneficial for treating diabetic polyneuropathies (see Chapter 20).

### *Ginkgo biloba*

*Ginkgo biloba* is a botanical with both antioxidant and antiplatelet activities. *Ginkgo biloba*'s antioxidant properties might make it useful in treating MS, given the importance of oxidative injury in MS. In addition, some investigators have suggested that its ability to block platelet activating factor (PAF) also might provide benefit in treating MS, since overproduction of PAF has been implicated in neurodegeneration[68]. One study reported a significant increase in both plasma and CSF levels of PAF in 20 MS patients compared to healthy controls[69]. This study also found that both plasma and CSF PAF levels were positively correlated with the number of active lesions on MRI. Treatment with PAF of rats in a model of MS, experimental autoimmune encephalomyelitis (EAE), increased disease severity, and treatment with a PAF antagonist isolated from *Ginkgo biloba*, ginkgolide B, suppressed the development of EAE[70,71].

There is one randomized, double-blind, placebo-controlled trial, evaluating the effects of ginkgolide B in the treatment of MS relapses[72]. A total of 103 patients experiencing a relapse of MS were randomized to one of three groups: placebo; ginkgolide B 240mg/day; and ginkgolide B 360mg/day. All patients were treated for 7 days. There were no statistically significant differences between the three groups, indicating that ginkgolide B is not an effective treatment for MS relapses. While this study was negative, one must be cautious in interpreting the results. The study focused on one constituent of *Ginkgo biloba*, which has antiplatelet but not antioxidant properties, and assessed only its effects on the treatment of relapses of MS. It is currently unknown whether *Ginkgo biloba* extract has any beneficial effects in controlling MS or limiting tissue injury.

Beyond its potential therapeutic effects as an antioxidant, *Ginkgo biloba* might be useful in treating cognitive dysfunction in MS. *Ginkgo biloba* has been shown to have a modest effect on cognitive dysfunction in Alzheimer's disease[73]. The mechanism of action is uncertain. Cognitive dysfunction is common among MS patients and an important cause of disability. There are no symptomatic therapies for this problem. One pilot trial of *Ginkgo biloba* in MS patients with cognitive dysfunction suggested that it might be beneficial . Further study of *Ginkgo biloba* as a symptomatic therapy for cognitive dysfunction in MS appears warranted.

## CONCLUSIONS

Despite MS patients commonly using a variety of CAM therapies and reporting benefit from some of these approaches, there is a paucity of well-designed clinical trials of CAM therapies in MS. The few randomized trials that have been performed, such as the trials of linoleic acid supplementation and ginkgolide B, have focused on the ability of these treatments to alter the disease course. However, patients primarily report symptomatic improvement and improvement in quality for life measures with CAM use, and there are

no published welldesigned randomized clinical trials on the use of any CAM therapies for symptomatic management in MS, although there are some pilot trials published as abstracts. Further clinical trials appear warranted on the effectiveness of a low-fat diet and ω-3 fatty acid supplementation used in combination with conventional therapies, such as recombinant IFN-β and glatiramer acetate, in decreasing disease activity. Investigating CAM approaches for symptomatic management of MS, such as the use of *Ginkgo biloba* for cognitive dysfunction and yoga and meditation for stress reduction, also appear to be indicated.

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# 18
# Non-prescription and non-pharmacological therapies for dementia

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*Complementary Therapies in Neurology: An Evidence-Based Approach*
Edited by Barry S.Oken
ISBN 1-84214-200-3 

Dementia is a common age-associated condition increasing in prevalence from about 1% at age 65 to over 50% above age 90. Dementia has many causes, some of which are easily treated (e.g. metabolic disturbances such as thyroid disease), while others have no treatments with a clear disease-modifying effect, such as the primary central nervous system degenerations[1]. The most common causes of dementia are Alzheimer's disease and vascular dementia and these will be the only two specific diseases in addition to the non-specific dementia syndrome discussed in this chapter; other dementia syndromes are not discussed because of the lack of specific data relevant to this chapter. The clinical onset of Alzheimer's disease is considered the time point at which there are signs of cognitive dysfunction in at least two domains of cognition (e.g. memory, attention, language, visuospatial function and 'frontal lobe' function) and the cognitive dysfunction is causing problems with daily social or occupational function. Before the cognitive deficits become so problematic, there is a period when the person may have some complaints of memory loss and objective deficits in memory or other cognitive domains but has no change in more than one domain and no change in daily function. This is considered mild cognitive impairment (MCI), although there are a host of other terms for closely related conditions (e.g. age-associated memory impairment). About 50% of people with MCI may go on to develop overt Alzheimer's disease over a 5-year period[2]. There is also a period even prior to the onset of MCI when there is accumulating pathology in the brain and there is possible subtle cognitive change. While this chapter does not review treatments for this latter class of individuals (basically all middle-aged adults), a significant proportion of the population believes that some dietary supplements may impact aging. A Harris poll of 1010 people in the USA found that 78% of the respondents felt that vitamin supplements would provide some or a great deal of help in generally healthy people in growing old and 58% felt the same way about herbs or herbal products[3]. There is a high use of dietary supplements including vitamins in the aging population. Even in healthy people over the age of 85 years, 25% take vitamin C supplements, 25% vitamin E supplements and 10% *Ginkgo biloba* extract[4].

## GINKGO BILOBA

There has been much work on basic science and clinical aspects of *Ginkgo biloba.* For further details on the basic science the reader is referred to two recent books and a review article[5–7]. Some of the following discussion on *Ginkgo biloba* is adapted from a previous chapter by the author[8].

### Rationale

*Ginkgo biloba* is a living fossil tree having undergone little change for over almost 200 million years. Extracts of the leaves have been used for 5000 years in traditional Chinese medicine for various purposes. Currently, most standardized *Ginkgo biloba* extract used for medicinal purposes is made from dried leaves and contains 24% flavonoids (primarily flavonolglycosides of kaempferol, quercetin and isorhamnetin) and 6% terpenoids. If using *Ginkgo biloba* extract one should avoid preparations that do not clearly state percentages. Although the extracts are standardized to these groups of chemicals, other compounds with biological activity are also present in *Ginkgo biloba* extract[9]. The terpenoids include bilobalide and the ginkgolides A, B, C, M and J (BN52020–BN52024) which are 20-carbon cage molecules with six 5-membered rings. The ginkgolides have some antioxidant properties and are antagonists of platelet activating factor (PAF), which has numerous biological effects[10]. Besides causing platelet activation and aggregation, PAF produces proinflammatory effects (e.g. vascular permeability), is an extremely potent ulcerogen in the stomach, and contracts smooth muscle, including bronchial smooth muscle. PAF has a direct effect on neuronal function and long-term potentiation[11,12]. It is unclear whether usual doses of current preparations of *Ginkgo biloba* extract provide enough biologically available active ingredients to impact PAF[10].

The other major components of *Ginkgo biloba* extract are the flavonoids including quercetin and kaempherol that contribute to ginkgo's antioxidant and free radical scavenger effects[13,14]. *Ginkgo biloba* extract or its components have been found to: reduce cell membrane lipid peroxidation in experimental spinal cord injury similarly to methylprednisolone[15]; reduce bromethalin-induced cerebral lipid peroxidation and edema[16]; protect brain neurons against oxidative stress induced by peroxidation[17–19]; decrease neuronal injury following ischemia or electroconvulsive shock[20]; reduce subchronic cold stress effects on receptor desensitization[21]; inhibit oxidative stress-induced platelet aggregation[22]; protect mitochondrial respiratory activity during hypoxia[23]; reduce hydroxyl radical induced apoptosis in rat cerebellar neurons[24]; decrease glutamate efflux in hypoxic/hypoglycemic rat cortical brain slices; and increase the survival of cultured embryonic spinal motoneurones[25]. More directly related to Alzheimer's disease, *Ginkgo biloba* extract partially prevented age-related morphological changes and indices of oxidative damage in rat mitochondria[26], attenuated memory decline associated with $\beta$-amyloid infusion in rats[27], prevented the $\beta$-amyloid-induced increase of reactive oxygen species[28,29], attenuate dapoptosis and inhibited $\beta$-amyloid aggregation in cell lines[30], inhibited beta-amyloid fibrillogenesis[30] and improved cognitive performance in aged mice[31] and in mice with cognitive impairments due to

scopolamine[32]. It has been reported that *Ginkgo biloba* extract improved learning and memory in a transgenic mouse model of Alzheimer's disease without altering the amyloid burden in the brain[33]. Altered gene expression for a number of proteins of potential relevance for Alzheimer's disease have been observed following *Ginkgo biloba* extract administration[34].

Therapeutically, *Ginkgo biloba* extract may be biologically plausible for use in Alzheimer's disease for at least two reasons. While the etiology of the common sporadic form of Alzheimer's disease is unknown and there are multiple pathophysiological processes involved in the disease, age-related oxidative injury and inflammatory processes may be important components. Since oxidative damage may play an important role in Alzheimer's disease pathogenesis or progression[35–37] and inflammation may be a contributor to the pathophysiology of Alzheimer's disease[38,39] *Ginkgo biloba* extract may be useful in treating the disease. There are other effects of *Ginkgo biloba* extract on neurotransmitter function and cerebral blood flow that have been less well studied than the antioxidant effects, but may also be of potential benefit in Alzheimer's disease.

## Evidence

### *Cognition*

There are dozens of studies mostly in the French and German literature suggesting the efficacy of *Ginkgo biloba* extract in mild to moderate memory impairment associated with aging, dementia or Alzheimer's disease, but only a limited number were properly blinded and placebo-controlled with adequate numbers of well-characterized subjects. Much of the difficulty with this literature relates to the use of the diagnosis 'cerebral insufficiency' that can be related to symptoms of depression and dizziness as well as to cognitive dysfunction. Some of this discussion is adapted from prior publications, including a meta-analysis[40] and a more recent systematic review[8]. In reviewing the ginkgo studies focusing on Alzheimer's disease, initially only five[41–45] out of over 50 studies were acceptable for analysis based on the following criteria:

(1) Sufficiently characterized patients such that it was clearly stated that there was a diagnosis of Alzheimer's disease by either the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) or National Institute of Neurological Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria, or there was enough clinical detail to determine the diagnosis by review;
(2) Clearly stated exclusion criteria including those for depression and certain central nervous system (CNS) active medications;
(3) Use of a standardized *Ginkgo biloba* extract in any stated dose for at least 1 month;
(4) Randomized, placebo-controlled and double-blinded study design;
(5) At least one outcome measure as an objective assessment of cognitive function.

Four of the five studies had sufficient statistical description of the data for meta-analysis (the study by Rai and colleagues[45] was the only paper excluded on this basis from the metaanalysis). In total there were 212 subjects randomized in these studies to placebo or *Ginkgo biloba* extract. A significant, but modest effect was found with *Ginkgo biloba* extract treatment (effect size 0.40; $p<0.001$). This effect size is exemplified in the two

largest studies by an Alzheimer Disease Assessment Scale-cognitive subtest difference of 1.7 in reference 43 and a Syndrom-Kurz Test difference of 1.5 in reference 44. It is of some interest that the study by Le Bars and colleagues has been criticized because of a very large 1-year dropout rate due to an atypical study design allowing subjects to opt for active treatment after 26 weeks. A reanalysis of their data at 26 weeks confirmed their effect with just a 21% dropout rate[46] and for the meta-analysis only the 26-week data were used. There was one additional paper published after the meta-analysis that would meet the inclusion criteria stated above (Table 1). It had similar results to the other studies and would not have affected the overall meta-analysis, especially given that there were only 20 subjects in total. A more recent 24-week trial involving 214 patients recruited from homes for the elderly with mixed diagnoses, including Alzheimer's disease, vascular dementia, mixed dementia and age-associated memory impairment without dementia, was negative[48]. This paper had differences from the above studies including the pooling of patients without a clear neurological diagnosis and elimination of subjects who had a placebo response during the 3-week run-in period.

There have been a number of papers evaluating the effect of *Ginkgo biloba* extract on objective measures of cognitive function in healthy volunteers with both single and chronic dosing experiments. Some have shown

**Table 1** Studies on the effect of *Ginkgo biloba* extract on Alzheimer's disease (AD). Adapted with permission from references 8 and 40

| *Study* | *Diagnoses* | *No. subjects analyzed* | *Study duration* | *Drop out rate (%)* | *Daily dose (mg)* | *Formulation* | *Cognitive outcome measures* | *Other outcome measures* |
|---|---|---|---|---|---|---|---|---|
| Hofferberth 1994[41] | AD | 40 | 3 months | ?5 | 240 | EGb 761 | SKT, choice reaction time | SCAGS, EEG |
| Kanowski *et al.*, 1996[44] | AD (DSM-III-R) | 125 | 24 weeks | 30 | 240 | EGb 761 | SKT | CGI, NAB, EEG |
| Le Bars *et al.*, 1997[43] | AD (DSM-III-R) | 207 | 26 weeks<br>52 weeks | 21*<br>56 | 120 | EGb 761 | ADAS-cog | CGIC, GERRI |
| Maurer *et al.*, 1997[47] | AD (DSM-III-R) | 20 | 3 months | 10 | 240 | EGb 761 | SKT, ADAS-cog, ZVT | CGI, EEG, ADAS-non-cog |
| Rai *et al.*, 1991[45†] | dementia with appropriate medical and psychiatric | 27 | 6 months | 9 | 120 | Tanakan | MMSE, Kendrick Digit Copying and Object Learning | EEG, P300 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | exclusions (?AD) | | | | | | tasks, digit recall, classification task | |
| Wesnes *et al.*, 1987[42] | dementia with appropriate medical and psychiatric exclusions | 58 | 12weeks | 7 | 120 | Tanakan | 10-item battery including Benton, Digit Symbol, word list recall, reaction time | Behavioral Rating Scale |

SKT, Syndrom-Kurztest; ADAS, Alzheimer Disease Assessment Scale (cog, cognitive subtest; non-cog, non-cognitive subtests); CGI, Clinical Global Impressions; CGIC, Clinical Global Impression of Change; NAB, Nurnberger Alters-Beobachtungsskala; SCAGS, Sandoz Clinical Assessment Geriatric Scale; GERRI, Geriatric Evaluation by Relative's Rating Instrument; ZVT, Zahlen-Verbindungs-Test (trailmaking)

*For 26-week data

†Met criteria for inclusion other than lack of sufficient statistics for meta-analysis

some positive effects[49–53] but the data are not consistent[54–56].

### *Clinical global impression of change*

There were insufficient data for formal metaanalysis. Le Bars and co-workers found no difference in their clinician global rating scale (mean Clinical Global Impression of Change was 4.2 in both groups)[43]. Kanowski and associates did find a difference in the percentage of subjects rated much improved or very much improved in the Clinical Global Impressions (32% in the *Ginkgo biloba* extract group and 17% in the placebo group, $p<0.05$)[57]. Maurer and colleagues, with only nine subjects completing the trial per group, found a nearly significant difference in the Clinical Global Impressions favoring the *Ginkgo biloba* extract group ($p=0.069$)[47].

### *Behavior and functional activity*

There were insufficient data for formal metaanalysis for either functional activity or behavior by itself. Le Bars and colleagues reported improvement in the Geriatric Evaluation by Relative's Rating Instrument, either as a mean treatment change (0.19 favoring *Ginkgo biloba* extract, $p<0.001$) or as a percentage of subjects improved (0.2 point change found in 37% of the *Ginkgo biloba* extract group and 23% of the placebo group, $p=0.003$)[43]. Kanowksi and associates reported no change in the Nurnberger Alters-Beobachtungsskala in terms of percentage of subjects who improved by at least two points (33% in the *Ginkgo biloba* extract and 23% in the placebo group, $p< 0.095$)[57]. Hofferberth reported statistically significant differences favoring *Ginkgo biloba* extract in all five subscales of the Sandoz Clinical Assessment Geriatric Scale: cognitive disturbance, emotional disturbance, lack of drive, social behavior and somatic

disturbance[41]. Wesnes and co-workers found no treatment difference in a visual analog scale of mood and alertness or in the Behavioral Rating Scale[42]. Maurer and colleagues found no difference among their 18 subjects in the Alzheimer Disease Assessment Scale (non-cognitive subscale)[47].

### *Appropriate patient population*

Inclusion criteria for studies have varied significantly. Ages have from ranged from as low as 45 years up to 90 years. Most studies included only subjects with mild or moderate impairments as assessed by screening cognitive tests or overall severity scores. Most of the exclusion criteria have listed significant medical illnesses, significant neurological illness other than dementia, depression and use of various CNS-active medications. Patients have generally had dementia of mild or moderate severity. There is no reported way to predict which patients will benefit from treatment.

## Clinical pharmacokinetics

The clinical pharmacokinetics of *Ginkgo biloba* extract are not well-defined in part because of the presence of multiple biologically active components. Serum concentrations of ginkgo flavonoids peak 2 to 3 h after ingestion and the half-life is between 2 and 4 h[58]. The half-lives of the terpenoid components (ginkgolide A, ginkgolide B and bilobalide) range from 3 to over 10 h[59]. The peak concentration of bilobalide is 2.3 h after oral administration[60]. In general, clinical studies have used dosing of two or three times per day.

## Adverse effects

In a previous review[58], no serious side-effects were noted in any of the older studies and the incidence of significant side-effects was similar in all the placebo-treated and ginkgo-treated groups. In the studies reviewed for the metaanalysis and the more recent studies there were no significant side-effects. In all these studies doses have ranged up to 240mg/day. While *Ginkgo biloba* extract is a PAF antagonist and could prolong bleeding time, at usual doses this is not necessarily the case[61]. A recent study directly assessing the effect of 240 mg/day of *Ginkgo biloba* extract on platelet function in a group of 28 healthy volunteers and 19 subjects with type 2 diabetes mellitus observed a significant effect of *Ginkgo biloba* extract on an objective measure of platelet function, although it was not clear how clinically significant this was[62].

There are now several case reports of hemorrhage in subjects who were taking *Ginkgo biloba* extract and these are summarized here. A 33-year-old woman had been taking 120 mg *Ginkgo biloba* extract for 2 years prior to developing bilateral subacute subdural hematomas without a known history of trauma[63]. Two simultaneously drawn bleeding times were 15 and 9.5 min with the upper limit for the laboratory being 9 min. One month after stopping *Ginkgo biloba* extract, two simultaneously drawn bleeding times were both 6.5min. A second case report concerned a 70-year-old man who had been taking daily aspirin for 3 years following coronary artery bypass surgery[64]. He developed spontaneous bleeding from the iris into the anterior chamber 1 week after beginning 80

mg daily of Ginkoba, a ginkgo extract. Another case concerned a 78-year-old woman on warfarin because of atrial fibrillation[65]. The subject also had a history of myocardial infarction, pacemaker insertion and progressive decline in gait and cognition. Two months after being seen for the cognitive decline, the patient developed a left parietal hemorrhage with a prothrombin time of 16.9 s and partial thromboplastin time of 35.5 s. The patient was taking *Ginkgo biloba* extract but the dose was not stated. A fourth patient developed a headache, backache and nausea for several days and was found to have xanthochromic cerebrospinal fluid with five red cells and one white cell and a protein level of 240 mg/dl[66]. Head computerized tomography (CT) scan without contrast and routine laboratory studies were normal, but the bleeding time was elevated (at 6 min, normal 1–3 min). He was found to have been taking *Ginkgo biloba* extract 40 mg 3–4 times per day for 6 months. His bleeding time went to 3 min after he was told to discontinue the *Ginkgo biloba* extract. The patient was considered to have had a subarachnoid hemorrhage. These case reports are not completely straightforward but are clearly of concern. However, given the very large number of people taking *Ginkgo biloba* extract and the lack of such serious side-effects reported in any of the published papers to date totaling several thousand subjects, the incidence of bleeding complications with ginkgo is of unknown magnitude and significance.

There are no definite contraindications to treatment. However, given the case reports of hemorrhage, the possible effect of *Ginkgo biloba* extract on platelet function and its only modest effect on cognitive function in Alzheimer's disease, caution should be used in patients with coagulopathies, those taking warfarin, or those with a history of significant hemorrhage. The risk of complications from *Ginkgo biloba* extract in people taking aspirin is unknown, but there is no evidence for aspirin being a definite contraindication.

## Starting, monitoring and stopping treatment

Most studies have not titrated the *Ginkgo biloba* extract dose and have started by using the desired final dose. There are no data on monitoring or stopping treatment. It is not known whether *Ginkgo biloba* extract produces its effect symptomatically or in a disease-modifying way. Thus, the absence of any improvement may not necessarily mean that there is no benefit, since its mechanism of action may allow it to alter the rate of progression (as opposed to the cholinesterase inhibitors whose effect is better understood and is primarily symptomatic).

## Future research

There are numerous unanswered questions about the utility of ginkgo in Alzheimer's disease. That there are so many unanswered questions about ginkgo probably relates to the development of its use through non-standard channels (outside the usual pharmaceutical companies). This has resulted in limited data from animal and human research even on basic issues such as dosing and toxicity. It remains uncertain whether there is an effect of *Ginkgo biloba* extract on non-cognitive function in Alzheimer's disease. This includes the overall clinical global rating scale, functional status or behavior. The definition of the types of subjects who may benefit from ginkgo is not

clear. The studies suggest some improvement in cognitive function in subjects with probable Alzheimer's disease of mild to moderate severity and probably in vascular dementia. The effect of *Ginkgo biloba* extract in possible or severe Alzheimer's disease, and other dementias is not known. The best dosing of *Ginkgo biloba* extract is not known. The studies reviewed here used a daily dose of 120 or 240 mg mostly divided three times daily, but also into two daily doses. It is not known whether the higher dose is better, or whether an even higher dose that has not been previously evaluated may be even better. Notably, many animal studies have used a dose of up to 50–150 mg/kg daily. It is not known whether twice daily dosing which would improve compliance is as good as the three times daily dosing used in most studies. The active ingredient or ingredients in *Ginkgo biloba* extract are not known. Is it one of the ginkgolides or is it the flavonoid component? If this were known, a more effective extract could possibly be developed. There are no data comparing efficacy of the various *Ginkgo biloba* extract preparations to clarify whether there are differences related to the specific process of extracting the ginkgo from the raw leaf. It is not known whether there is a low incidence of significant complications, e.g. bleeding. If this is an issue, the relative contraindications, such as use of other antiplatelet agents or history of gastrointestinal bleeding, could be defined. Lastly, as with all botanicals, issues related to standardization are not straightforward (see Chapter 2). The precise chemical constitution of the drug may vary with age of the tree and season, and the current standardization to flavonoid and terpenoid totals may not reflect the most relevant active ingredient or ingredients[67]. Additionally, as with all botanicals, the standardization stated on the label may not reflect the actual content[68–70] (Table 2).

**Summary**

There is an effect of *Ginkgo biloba* extract on cognitive performance in Alzheimer's disease, although the effect is fairly modest. Recent

**Table 2** Analysis of off-the-shelf brands of *Ginkgo biloba* extract for components thought to contain 24% flavone glycosides and 6% terpene lactones. Adapted with permission from reference 70

| *Product* | *Flavone glycosides (%)* | *Terpene lactones (%)* | *Cost per pill (cents)* |
|---|---|---|---|
| American Fare Vita-Smart | 23.2 | 7.6 | 11 |
| Health's Finest | 28.4 | 10.9 | 22 |
| Lichtwer Pharma Ginkai | 26.0 | 9.9 | 30 |
| Natural Brand | 24.3 | 8.8 | 21 |
| Nature Made | 29.1 | 6.4 | 40 |
| Nature's Resource | 25.8 | 9.2 | 18 |

| | | | |
|---|---|---|---|
| Nature's Way Ginkgold | 22.9 | 6.9 | 35 |
| Pharmanex BioGinko | 25.4 | 7.7 | 28 |
| Pharmaton Ginkoba | 23.7 | 8.2 | 31 |
| Rite Aid | 25.6 | 9.3 | 25 |
| Sundown Ginkgo Alert | 22.2 | 9.8 | 23 |
| Your Life | 27.9 | 9.9 | 22 |

American Academy of Neurology practice parameters for management of dementia indicated that there were only inconclusive data on the effect of ginkgo on cognitive function and considered it a practice option[71]. This conclusion is slightly more negative than the data suggest[72,73]. The cognitive changes are of a similar magnitude or slightly less than those reported for the currently available cholinesterase inhibitors. There is limited or inconsistent evidence for the effect of *Ginkgo biloba* extract on daily function, behavioral disturbance or clinical global rating scales. There is no evidence concerning quality of life or delay of nursing home placement. The value of treatment with *Ginkgo biloba* extract is unknown in patients with possible Alzheimer's disease, very mild dementia or severe dementia, and other dementias (with the possible exception of vascular dementia). As with other botanicals, the purity and potency of a given preparation is not as well controlled as those of conventional medicines. The correct dose is uncertain with a total daily dose of 120–240 mg standardized ginkgo extract having been used in most studies. There have been case reports of bleeding complications in patients taking ginkgo for various reasons but, owing to the very large numbers of people taking *Ginkgo biloba* extract and the lack of clear monitoring in most of these patients, it remains uncertain whether there is a higher risk for bleeding complications. Given its mode of action on PAF it certainly seems prudent to advise against its use in patients receiving anticoagulants.

## VITAMIN E

Vitamin E is a fat-soluble, naturally occurring, essential vitamin. 'Vitamin E' includes a group of related chemicals of which naturally occurring α-tocopherol is the most important for humans. The current Institute of Medicine recommended dietary allowance for natural α-tocopherol, which is also referred to as RRR-α-tocopherol or D-α-tocopherol, is 15mg or 22.5 International Units (IU). Dietary supplements containing vitamin E are either natural or synthetic. If one is utilizing synthetic (all racemic or DL-α-tocopherol, a dose of 33 IU would be needed to obtain the 15 mg of natural D-α tocopherol (a conversion factor of 0.45). For natural α-tocopherol, one would multiply the amount in IU by 0.67 to obtain the natural α-tocopherol in mg.

The rationale for considering vitamin E in Alzheimer's disease includes data that oxidative injury plays a role in the disease[36,74]. There is some evidence that there are lower plasma or cerebrospinal fluid levels of α tocopherol in patients with Alzheimer's disease than in controls, and that vitamin E level may be inversely correlated with cognitive function in non-demented seniors, although the data are not consistent[75–79].

## Evidence

There are a number of studies looking at the intake of vitamin E from an epidemiological perspective on either age-related cognitive decline or on the development of Alzheimer's disease in both cross-sectional and prospective studies[80–87] (Table 3). The effect of vitamin E supplementation on cognitive decline or incident dementia in these epidemiological studies has been inconsistent and more studies have been negative than positive. The effect of intake of vitamin E from foods on these same outcome measures has been more consistently positive, but this is also inconsistent.

Although there is a suggestive finding of an association between vitamin E intake from foods and development of Alzheimer's disease, there is a major limitation of all epidemiological studies described in this section as well as others. There is a group of health-promoting behaviors, currently known and unknown, that co-vary with each other and are not easily addressed without a prospective randomized intervention trial. Although years of education is statistically addressed in all these vitamin E studies, other behaviors that may impact on development of Alzheimer's disease ranging from physical activity and mental stimulation to dietary intake of other vitamins and other food constituents such as omega-3 fatty acids are generally not addressed. In one prospective population-based study, baseline Minimental State Examination (MMSE) was significantly correlated with flavonoid intake[86]. Vitamin E intake from food may co-vary with numerous other potentially beneficial chemicals in food besides omega-3 fatty acids. People with low vitamin E intake from foods my have low intakes of other potentially relevant substances such as folate. Additionally, there are potential problems obtaining historical data from food frequency questionnaires from subjects with incipient Alzheimer's disease. Subjects may have inaccurate recall and subjects who notice some memory decline may begin to take dietary supplements[88].

The clinical trial data regarding vitamin E in Alzheimer's disease are very limited. Vitamin E supplementation does increase concentrations in the cerebrospinal fluid in patients with Alzheimer's disease, although the antioxidant effect as measured by lipid hydroxides may be greater when combined with vitamin C[89]. There has been a single prospective clinical trial of vitamin E in Alzheimer's disease as part of a large multicenter trial of vitamin E and selegiline[90]. Vitamin E (DL-α-tocopherol) in a dose of 2000 IU/day was reported to delay a combined clinical measure of worsening (time to nursing home placement, conversion to a Clinical Dementia Rating scale of 3, significant decline in activities of daily living, or death) compared with placebo. There was no effect on cognitive function. It is of interest that the uncorrected, first-pass data analysis revealed no significant ($p$>0.05) beneficial effect of vitamin E on the primary combined outcome measure. After correction for a slight baseline difference among the four groups in MMSE ($p$=0.1), the selegiline, vitamin E and combined groups had slightly better outcomes as defined by the combined outcome measure death, nursing home placement, conversion to Clinical Dementia Rating score 3 or decrease in activities of daily living. Concerns about the analysis have been raised[91]. Additionally, there were no significant effects on cognitive measures in the study, certainly raising the possibility that any poorly defined effect of vitamin E on the outcome measure may have nothing specifically to do with Alzheimer's disease. While the combined outcome measure has public health implications, it is affected by types of behaviors and clinical events other than severity of Alzheimer's disease that contribute to nursing home placement and death, e.g. aggressive

behaviors, extrapyramidal signs, incontinence, vascular disease and socioeconomic status. It could be argued that all

**Table 3** Epidemiological studies relating intake of vitamin E from diet and supplements with age-related cognitive decline or the development ofAlzheimer's disease (AD)

| | *No. studied (no. developing AD or dementia* | *Age rang (years)e* | *Follow-up period if longitudinal* | *Vitamin E assessment* | *Outcomes* | *Results* | *Statistical adjustment factors* |
|---|---|---|---|---|---|---|---|
| Warsama Jama *et al.*, 1996[80] | 5182 | 55–95 | cross-sectional | FFQ + supplement use | MMSE <26 | no effect of total vitamin E | age, education, sex, smoking, caloric intake, intake other antioxidants |
| Morris *et al.*, 1998[82] | 633(91) | 65+ | 4.3 years | supplement use | incident AD | effect with vitamin E supplements | sex, education, length of follow-up |
| Masaki *et al.*, 2000[84] | 3385 | 71–93 | cross-sectional | supplement use | prevalent dementia and cognitive change | vitamin E decrease VD, no effect AD | education, history of stroke, APOE, |
| Morris *et al.*, 2002[81] | 815(131) | 65+ | 3.9 years | FFQ + supplement use | incident AD | effect with vit E intake from FFQ but not from supplement | age, education, sex, race, APOE, length of follow-up |
| Morris *et al.*, 2002[83] | 2889 | 65–102 | 3.2 years | FFQ + supplement use | cognitive change per year | effect with vitamin intake total or food only, but not for vitamin E just from supplement | age, race, sex, educational level, current smoking, alcohol use, caloric intake |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | | | | | vitamin supplement use |
| *Laurin et al.*, 2002[85] | 2369(222) | 71–92 | 5.2 years | supplement use | incident dementia | effect, (longitudinal analysis of Masaki *et al.*, 2000 cohort[84]) | year of birth, education, APOE, smoking, alcohol use, body mass index, caloric intake |
| Engelhart *et al.*, 2002[86] | 5395 | 55+ | 6 years | FFQ | incident dementia and AD | effect of vitamin E intake from FFQ with full adjustment, not just adjusted for age, sex, MMSE, and alcohol | age, sex, baseline MMSE, alcohol, education, smoking, BMI, caloric intake, presence of cartotid plaques, APOE, and use of antioxidant supplements |
| Luchsinger *et al.*, 2003[87] | 980 | 65+ | 4.0 years | FFQ + supplement use | incident AD | no effect | age, gender, education, smoking, APOE, ethnic group |

FFQ, food frequency questionnaire; APOE, apolipoprotein E genotype; MMSE, Mini-mental state exam; VD, vascular dementia; BMI, body mass index

these factors should have been covariates in the analysis.

There were no adverse events clearly attributable to vitamin E in the single Alzheimer's disease trial using 2000 IU/day. The Institute of Medicine has set 1000 mg/day as the tolerable upper limit[92], meaning that any dose below this is considered safe and there are no reliable safety data at doses about this limit. There are potential bleeding risks at very high doses. There have been at least two lower-dose trials for conditions other than dementia where there was some increased morbidity from doses below the tolerable upper limit, although it is uncertain whether these were actually causally related[92,93].

### Summary

Recommendations regarding vitamin E and Alzheimer's disease are based on very limited clinical trial evidence. A formal independent assessment of vitamin E by the Cochrane Collaboration concluded that 'there is insufficient evidence of efficacy of vitamin E in the treatment of people with Alzheimer's disease'[94]. A recent *New England Journal of Medicine* article reviewing vitamin therapy considered the data for vitamin E use for Alzheimer's disease as sparse[95]. The suggestion to use 2000IU vitamin E in patients with Alzheimer's disease may be reasonable, but to consider it as reflecting moderate clinical certainty as suggested by the American Academy of Neurology (AAN) practice parameter[71] is overstating the evidence[72] . It is unclear what is the correct dose of vitamin E to use in Alzheimer's disease. Effects on bleeding parameters may be seen at 2000 IU, but doses on the order of the current routine dietary allowance probably do not produce sufficiently high brain levels to have an impact. Doses over 1000 IU should be used very cautiously in people taking warfarin, because of vitamin E's ability to increase the International Normalized Ratio in those on warfarin. Owing to vitamin E's widespread availability and its relative safety, it may not be feasible to perform another large, multicenter placebo-controlled study of its use in Alzheimer's disease in the USA. There is an ongoing trial of its use in mild cognitive impairment. However, given the concerns regarding oxidative damage with aging along with the safety and low cost of vitamin E, it is not unreasonable to recommend vitamin E supplementation in patients with Alzheimer's disease, although it should be reiterated that there are no data to suggest any change in cognitive function. The ideal dose is unclear, but it probably needs to be higher than the 400 IU often suggested by cardiologists. Vitamin E should be used cautiously in people taking warfarin and people with low vitamin K, because of potential interactions and enhancement of an anticoagulant effect. There is no documentation of complete safety at doses of 2000 IU/day.

## VITAMIN C

Better cognition in seniors or lower incidence of Alzheimer's disease has been correlated with higher vitamin C levels[77,96] and higher intake of vitamin C[82,86,97], although the data are not consistently positive[75,76,78,80,81,85,87]. In Alzheimer's disease, there have been reported to be low levels of ascorbate in cerebrospinal fluid[98] and increasing severity of illness may correlate with lower vitamin C levels despite adequate vitamin C intake[99]. There are no specific data in Alzheimer's disease to suggest that it may be useful in terms of improving cognition or function, although there are some data to suggest that adding vitamin C to vitamin E supplementation may be beneficial in terms of maximizing the beneficial effects of vitamin E on *in vitro* lipoprotein oxidation[89].

## OTHER VITAMINS

While there are some small studies that claimed significant benefit from high-dose thiamine[100,101], other studies[102] and a recent Cochrane review[103] found limited evidence

from their systematic review that thiamine was a useful treatment for Alzheimer's disease. There is no reason to recommend thiamine for patients with Alzheimer's disease.

There are some epidemiological data that suggest that low vitamin $B_{12}$ and folate levels may be associated with an increased incidence of Alzheimer's disease[104], but there is no evidence from any treatment trials. As with all people, but especially elders, it is important to ensure an adequate intake of folate through appropriate diet or as part of a vitamin supplement.

## LECITHIN AND CITICOLINE

One of the more prominent neurochemical defects in Alzheimer's disease is a decrease in acetylcholine, associated with degeneration of basal forebrain cholinergic nuclei in most cases. The current prescription drugs approved for use in Alzheimer's disease by the US Food and Drug Administration are acetylcholinesterase inhibitors. It was thought that another way to increase brain acetylcholine was administering precursors necessary for its synthesis. Phosphatidylcholine is a phospholipid that is the major dietary source of choline. Its administration increases levels of choline better than administration of choline by itself. Phosphatidylcholine is also crucial for cell membrane structure and function. Lecithin chemically is considered to be the same as phosphatidylcholine but when offered commercially it often refers to a mix of lipids that contain phosphatidylcholine. There have been a number of clinical trials of lecithin in Alzheimer's disease, both as add-ons to clinical studies of tacrine, a cholinesterase inhibitor, and as studies of lecithin by itself. Theoretically it would appear to be difficult to increase brain acetylcholine by administering lecithin, because it is not a rate-limiting step in its synthesis. The lecithin studies as a group have not been particularly promising. A recent Cochrane review found no evidence to support the use of lecithin in Alzheimer's disease[105]. Citicoline (CDPcholine) is another naturally occurring substance that is an intermediate metabolite in the synthesis of phosphatidylcholine. There have been phase III trials in stroke but only several short-term trials in older individuals and in those with dementia. The trials have been generally positive resulting in a Cochrane systematic review suggesting that there is some evidence of citicoline having a positive effect, at least in the short term[106], although larger trials and those with longer duration are needed.

## DEHYDROEPIANDROSTERONE

Dehydroepiandrosterone (DHEA) and its sulfate (DHEAS), are the most abundant hormones in the human body. They are synthesized in the adrenals and their levels decrease significantly with aging, attaining levels at age 80 years only 20% of those seen at age 20[107,108] DHEA is a precursor for biosynthesis of other sex steroids, testosterone and estrogen, and is itself a weak androgen. DHEA and related metabolites have been found in all areas of the brain, and its metabolism may be altered in Alzheimer's disease[109]. Its precise function and mechanism of action are not known, although it may be a counterregulator of glucocorticosteroids. There are a number of non-human studies suggesting that DHEA replacement may improve some age-related declines in areas such

as immunosenescence and osteoporosis. However, there are very limited human studies addressing its long-term risks or benefits. There has been no significant short-term toxicity in humans when the supplemental dosages were adjusted to keep serum DHEA levels within normal physiologic limits. There have been several clinical studies in healthy elders that have not demonstrated any consistent positive effect[110–113] on cognitive function. Recent studies do not support prior preliminary findings that low DHEA or DHEAS levels were associated with Alzheimer's disease and other forms of cognitive dysfunction among elders[114,115], although there remains the possibility that DHEAS is non-specifically reduced in dementia[116]. One Alzheimer's disease study actually found lower DHEA levels unexpectedly associated with better performance on the Alzheimer's Disease Assessment Scale (ADAS) and MMSE[117]. A recent study of 58 subjects with Alzheimer's disease found no statistically significant improvements in cognitive function or overall measure of change at 6 months with DHEA 50 mg twice a day compared to placebo. However, there were some trends towards benefit at 3 months, and the study may have been underpowered to detect the over 4-point difference in ADAScognitive subtest that was seen at 6 months[118]. In summary, there are essentially no data demonstrating proven benefit for DHEA in Alzheimer's disease[110]. If one is contemplating using DHEA it should be done under medical supervision, and blood levels should be monitored to ensure that only physiologic levels are attained.

## ACETYL LEVOCARNITINE (L-ACETYLCARNITINE)

Acetyl levocarnitine is structurally similar to acetylcholine and may also have a role in protection from oxidative damage. There have been at least six controlled studies of its use in Alzheimer's disease published in English (e.g. reference 119). While most reported that the drug group did slightly better than the placebo group, there have been two large subsequent trials. One multicenter trial of over 400 patients did not report any difference, although it raised the possibility that patients under the age of 65 years may have benefited from the drug, while those over 65 years may have done worse[120]. Another large multicenter trial was also negative in the outcome measures in intention-to-treat analysis, although in the analysis of only those completing the study there was less deterioration in one of the secondary outcome measures, the MMSE, in the treatment group[121]. The doses used in the studies have ranged from 1.5 to 3 g/day. No clear side-effects have been noted. Acetylcarnitine is of questionable benefit, and in one trial may have worsened the symptoms of Alzheimer's disease among older patients.

## PHOPHATIDYLSERINE

Phophatidylserine is a component of cell membranes and probably has multiple functions. There have been several controlled trials in Alzheimer's disease and age-associated memory impairment[122–126]. Initial trials were positive but later studies were not so positive. To date its utility for treatment of Alzheimer's disease is uncertain.

## MELATONIN

Patients with dementia, including Alzheimer's disease have disturbances in circadian rhythm that may be partially related to known melatonin secretion changes[127–129]. Melatonin also functions as an antioxidant. Melatonin has been suggested as a useful adjunct to treatment for disturbed behaviors that may be secondary to circadian rhythm dysfunction[130]. Doses of melatonin generally ranging from 2.5 to 6 mg taken in a single dose 30–120 min prior to bedtime may be of some benefit in managing sleep disturbances or 'sundowning' symptoms related to Alzheimer's disease[131–135], although the results have not been consistent[136,137]. The largest trial evaluating melatonin in 157 patients with Alzheimer's disease found no effect on sleep[138]. The melatonin was well tolerated. Although melatonin may have helped some people in the trial, as evidenced by a trend in the expected direction, it does not have a clearly potent or predictable effect on sleep. Its effect on behavioral symptoms, possibly related to circadian rhythm dysfunction, has not been fully evaluated.

## FATTY ACIDS

The brain has a high lipid content that comprises over half the dry weight of the brain[139]. Essential fatty acids are critical for normal neuronal function and integral for numerous cellular functions especially those related to membrane function. There is a change in human brain lipid composition associated with aging and Alzheimer's disease[140,141] and evidence in animals that this lipid composition change is associated with age-related cognitive changes[142].

Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are polyunsaturated omega-3 fatty acids obtained from certain fish such as mackerel, herring and salmon, that are of some benefit in cardiovascular disease[143]. Other omega-3 fatty acids such as α-linolenic acid may be found in plant-derived products such as flaxseed oil. Supplementation with DHA may ameliorate cognitive declines associated with aging in mice[144,145], decrements in learning associated with amyloid infusion in rats[146] and declines in passive avoidance performance in stroke-prone hypertensive rats[147].

In humans, there are limited clinical trials. There are cross-sectional epidemiological studies that suggested that higher fish intake, omega-3 fatty acid intake or plasma omega-3 levels may be related to a lower incidence of cognitive decline and dementia[148–153]. These epidemiological data may be related to the association between fish intake and vascular disease, including decreased stroke rates[154]. Another epidemiological study found that an increased risk of developing Alzheimer's disease was associated with a greater intake of saturated fat and of *trans*-unsaturated fat, the latter a result of partial hydrogenation of vegetable oils[155]. A4-week trial of an omega-3 preparation in 100 Alzheimer's disease patients suggested that there were no significant adverse events with its use other than a much higher incidence of diarrhea. Most guardian ratings in 12 areas ranging from memory and spatial orientation to daytime alertness and sleep problems were improved in the treatment compared to the control group[156]. Issues with blinding were not mentioned and no ratings or evaluations other than guardian ratings were performed. A non-blinded 1-year trial in 20 patients with vascular dementia found

relative benefit of DHA on psychometric tests[157]. While omega-3 fatty acids are beneficial for general health reasons, there are no clear data pointing to their utility specifically for dementia.

## OTHER ORTHOMOLECULAR AND HERBAL REMEDIES

There are a large number of agents that have been tested in limited clinical trials or animal experiments. Although oxidative injury may be important in the pathogenesis of Alzheimer's disease, there are no significant clinical data on other antioxidants (e.g. zinc and selenium). A specific extract from cat's claw *(Uncaria tomentosa)* was found to inhibit amyloid fibrillogenesis *in vitro* and in preliminary animal studies[158]. Huperzine A is a potent cholinesterase inhibitor that has been used in China, but the clinical data are very limited[159–161]. A large American trial is currently planned. Coenzyme Q is an antioxidant that is an essential cofactor of the electron transport chain and has potential for treatment of neurodegenerative disorders[162]. There is evidence for benefit from a human trial in Parkinson's disease (see Chapter 19), but there are no clinical data for Alzheimer's disease. A single small trial of vinpocetine demonstrated no efficacy for Alzheimer's disease[163], although there are some animal and *in vitro* data suggesting potential benefit[164,165]. There wasa single well-designed trial of 50 mg/kg per day *N*-acetylcysteine in 43 patients with probable Alzheimer's disease that did not demonstrate effects on the primary outcome measures of MMSE score and an activities of daily living scale, but there were changes in some of the secondary measures[166]. Curcumin, the main yellow pigment in turmeric, has antioxidant properties[167,168] and, in the amyloid precursor protein Alzheimer's disease mouse model, this has been shown to reduce oxidative damage, $\beta$-amyloid and plaque burden[169]. *Salvia officinalis* (sage) has been reported to have beneficial effect in a single double-blind placebo-controlled trial in 42 patients with mild to moderate Alzheimer's disease using the ADAS-cognitive subtest and Clinical Dementia Rating (CDR) scale Sum of the Boxes[170]. Choto-san, a traditional Japanese medicine, had some beneficial effect on global ratings as well as on functional measures in patients with vascular dementia as diagnosed by defined criteria and using imaging studies[171]. These investigators also found that the main ingredient in Choto-san, *Uncaria sinensis*, was protective in glutamate-induced cerebellar granule cell death. Nicotine skin patches had some beneficial effect in a placebocontrolled crossover trial of eight subjects with Alzheimer's disease as assessed by a continuous performance task, but there was no improvement on measures of memory function[172]. Pyritinol, a pyridoxine derivative, was reported to be useful in Alzheimer's disease as well as vascular dementia in a randomized trial of 164 patients using standard cognitive and functional outcome measures[173]. There was an earlier trial also reporting positive effects in 40 hospitalized patients with modestly severe dementia[174], but no more recent large trial. Various forms of aromatherapy have also been evaluated for management of behavioral symptoms in dementia with some benefit reported in pilot studies[175–181].

Extracts of *Bacopa monniera* have been used in ayurvedic medicine as a cognitive enhancer. It appears to induce antioxidant activity in the brain[182] and produced some protection from scopolamine- and phenytoin-induced cognitive deficits in mice[32,183]. There have been small trials in healthy humans suggesting some beneficial effect on

cognitive function[184,185], although another small study found no effects on cognitive function from a single dose of bacopa along with *Ginkgo biloba* extract[56]. No large trials or trials in Alzheimer's disease have been performed.

Other herbals with wide use have not been well-studied in Alzheimer's disease (e.g. ginseng and green tea) and thus there are no data to support their use. St John's wort has been studied in clinical trials of depression with some evidence of effectiveness for treatment of mild to moderate depression (see Chapter 25), but it has not been specifically studied in Alzheimer's disease.

## MIND-BODY TECHNIQUES (YOGA, MEDITATION, TAI CHI)

There have been several reports of improved performance with these mind-body techniques. Some aspects of these interventions are also discussed in Chapter 9. Yoga is an ancient Indian, non-religious, mind-body approach that has components centering around meditation, breathing and activity or postures. The active yoga or Hatha yoga techniques are probably the most common type practiced in the USA. It is a non-competitive system for development of physical and mental well-being through stretching of all muscle groups for strength, flexibility and physical balance. A person assumes a series of stationary positions that utilize isometric contraction and relaxation of different muscle groups to create specific body alignments. There is also a deep relaxation component. Some types of Hatha yoga are amenable to easy adaptation for elders or those with neurological limitations through modifications of the poses and the use of props such as blankets and chairs[186,187]. Hatha yoga has been reported to produce improvements in mood comparable to aerobic exercise[188,189]. However, there may be no effect on cognitive function. A well-designed study from Duke University compared a 16-week aerobic exercise intervention or yoga group to controls in elders. The study revealed no differences in several cognitive measures including a divided attention task and a Sternberg-type visual search task, despite some improvement in self-rated general mood and psychiatric variables[190–192]. This study was designed primarily to look at the effect of exercise intervention on physiological and psychological measures in elders, since prior exercise studies produced mixed results[193,194]. The yoga intervention was intended merely to provide 'a control for the effects of social stimulation and attention from trainers without producing an aerobic training stimulus'. Thus, it is unclear whether the yoga intervention was adequate since it was so poorly described. A controlled trial of meditation in elders (mean age 81), many not living independently, produced improvements in a measure of cognitive flexibility and a trend towards improvement in ability to focus attention as measured by the Stroop Color and Word Test[195].

There have been recent trials suggesting that tai chi practice in elders may improve several outcomes including balance, physical function and functional mobility[196–198], but not necessarily in those living in a long-term care facility[199]. A group of healthy elders practicing tai chi performed better than controls on tests of posture control, namely timed one-leg standing[200]. There is a large current trial to study the effect of tai chi in reducing falls among older adults[201].

While yoga, tai chi and meditation probably have some beneficial general health effects, there are no reliable data to suggest specific efficacy in dementia.

## ACUPUNCTURE

There have been at least two papers concerning acupuncture and traditional Oriental medicine but no controlled studies[202,203].

## CONCLUSIONS

Most of the alternative therapies for dementia and Alzheimer's disease described above have not been the subject of high quality clinical studies with reproducible results. As a rule, conventionally trained physicians should inquire about complementary therapies used by patients in order to be aware of potential drug interactions and to ensure that the patient feels comfortable discussing complementary and alternative medicine (CAM) therapies with their non-CAM health-care provider. Patients may need to be specifically asked about dietary supplements and non-prescription medications, since they do not necessarily volunteer this information, even on a written questionnaire[204]. In general, when considering complementary therapies, it should be ensured that patients are actually taking what is recommended. Some of these products are not of pharmacy grade, do not contain known amounts of the intended drug and may contain unknown amounts of other drugs. Taking relatively pure, known amounts of the drug under consideration should be attempted. Given the clinical trial data, as well as their relatively low cost and risk, the use of *Ginkgo biloba* extract and vitamin E supplements should be strongly considered. There are significantly less data and rationale for use of other complementary therapies even though they have relatively low risk and cost. Some, such as yoga and tai chi, are non-specific health-promoting strategies and some, such as citicoline and phosphatidylserine, have had some preliminary positive results.

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# 19
# Evidence-based complementary and alternative medicine in Parkinson's disease

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*Complementary Therapies in Neurology: An Evidence-Based Approach*
Edited by Barry S.Oken
ISBN 1-84214-200-3 

## CLINICAL FEATURES OF PARKINSON'S DISEASE

James Parkinson first described Parkinson's disease and its distinctive features of tremor and gait difficulties in 1817[1]. More than 100 years later, Greenfield and Bosanquet[2] published the most complete description of the selective cell loss, depigmentation and degeneration of the substantia nigra. About 10 years later, it was discovered that dopamine was depleted in Parkinson's disease and that levodopa, as the precursor to this neurotransmitter, could improve Parkinson's disease signs; these results were described in landmark studies[3,4].

Parkinson's disease is a common movement disorder and affects approximately 500000 people in the USA[5]. It is most frequently seen after the age of 50, and approximately 1% of this age group has the disorder. The cardinal features of Parkinson's disease include resting tremor, bradykinesia (slowness of movement), rigidity (stiffness) and postural instability. Additional signs that help the clinician to diagnose Parkinson's disease are marked asymmetry of parkinsonian signs, a clinically significant response to levodopa and few or no balance problems in the first months and years of the disease[6]. The pattern of asymmetry may persist throughout the disease. Patients with moderate or advanced Parkinson's disease experience increasing gait difficulty, bradykinesia and tremor. After 5 years of treatment for Parkinson's disease, many patients will develop motor fluctuations, dyskinesias and behavioral or cognitive changes.

The behavioral and cognitive problems experienced by patients include fatigue, depression, dementia, hallucination and excessive daytime sleepiness. Fatigue may be one of the most disabling symptoms for patients with PD, but has so far drawn little attention. Lou and co-workers[7] reported that about two-thirds of 39 patients studied suffered either abnormal physical fatigue, mental fatigue or both. Depression occurs in approximately one-third of patients, especially in those patients who have akinesia and rigidity as their predominant symptoms[8]. Dementia occurs in approximately one-third of patients and hallucinations and psychotic behavior in approximately one-fourth of chronically treated patients.

Parkinson's disease may have a multifactorial cause, but might involve free radical toxicity from oxidative reactions[9]. Free radicals react almost instantaneously with membrane lipids and cause lipid peroxidation, membrane injury and cell death[10]. Dopamine is metabolized by oxidation reactions capable of generating free radical byproducts. The selective degeneration of nigral cells in Parkinson's disease may be attributed to the high levels of iron and decreased levels of glutathione in the substantia nigra of patients[11].

There are two distinct theoretical approaches for treating Parkinson's disease: to arrest the disease progression or to provide effective symptomatic therapies. Unfortunately, no treatment to date can arrest the disease progression. However, several effective symptomatic therapies are available. Although the therapeutic approach varies among clinicians, treatment algorithms have been developed by expert panels[12]. Anticholinergics such as trihexyphenydil are effective in treating mild tremor in young patients and amantadine can be used for mild bradykinesia, rigidity and gait disturbance. In early or mild Parkinson's disease, dopamine agonists are used as monotherapy, and in more advanced disease they serve as adjuncts to carbidopa/levodopa. Bromocriptine, pergolide, pramipexole and ropinirole are four dopamine agonists that are currently available in the USA. Dopamine agonist therapy reduces the prevalence of motor fluctuations compared to treatment with levodopa alone[13]. Carbidopa/levodopa remains the most potent and reliable drug used for treating the symptoms of Parkinson's disease. Clinicians often initiate levodopa therapy when symptoms start to interfere with patients' activities of daily living. Two catecholamine-*O*-methyl transferase (COMT) inhibitor agents, entacapone and tolcapone, increase the bioavailability of peripheral levodopa[14,15] and reduce motor fluctuations[16]. Neurosurgical treatments such as subthalamic stimulation, pallidal stimulation, thalamic stimulation and thalamotomy have emerged as new experimental possibilities for advanced Parkinson's disease[17] . These procedures are generally reserved for subjects with advanced Parkinson's disease and motor fluctuations, usually without other clinically significant medical conditions[18]. The major goals are to improve motor function and to reduce motor fluctuations and dyskinesia.

## THE USE OF COMPLEMENTARY AND ALTERNATIVE MEDICINE

Rajendran and colleagues[19] surveyed 201 Parkinson's disease patients and found that about 40% of the Parkinson's disease patients they surveyed used at least one form of complementary and alternative medicine (CAM). They administered a structured questionnaire, by interview, regarding the use of CAM in these patients. Vitamins, herbs, massage and acupuncture were most commonly used. Younger patients and those patients with a younger age at onset of Parkinson's disease were more likely to use CAM. In addition, patients who used CAM had higher incomes and educational levels. Most importantly, the use of CAM was not associated with disease severity, disease duration, levodopa treatment duration, surgery for Parkinson's disease or motor fluctuation. Only 12% of these patients used CAM before the diagnosis of Parkinson's disease. More than half of those patients who used CAM did not inform their physicians about this use.

Rajendran and co-workers[19] did not ask the patients why they used CAM. However, Astin[20] investigated the reasons patients used CAM in the general population. He found

that patients do not use CAM because of their dissatisfaction with conventional treatment. Most patients, like Parkinson's disease patients, used CAM in conjunction with, rather than as an alternative to conventional therapy. He also found that patients do not use CAM because of the need for personal control or autonomy in health-care decisions. Instead, he found that the best predictors for the use of CAM was a patient's philosophical congruence, including a holistic orientation to health or a transformational experience to change one's world view. Rajendran and colleagues[19] suggested that the diagnosis of Parkinson's disease may represent such an experience, which may explain why the use of CAM increased more than three-fold (from 12% to 40%) after the diagnosis of Parkinson's disease in their population.

## THE EFFECTIVENESS OF COMPLEMENTARY AND ALTERNATIVE MEDICINE

We have conducted an extensive Medline search using the key words 'Parkinson's disease' cross-referenced with one of the following key words: acupuncture, Alexander technique, alternative medicine, alternative therapy, complementary therapy, chiropractic, EDTA chelating, electromagnetics, electrotherapy, ginkgo, herb, hypnosis, lipoic acid, massage therapy, music therapy, physiotherapy, Qi Gong, reflexology, Tai Chi, melatonin, meditation and Yoga. We searched Medline from 1966 to December 2002. It became apparent that the number of CAM therapies that have been used to treat Parkinson's disease is quite large. However, only a handful of studies have examined the effect of CAM in a well-controlled manner and could validate its effectiveness.

## THE DATATOP STUDY

Vitamin E, or tocopherol, is one of the fatsoluble vitamins. Vitamin E includes several structurally related compounds with varying biological activities such as α, β, δ, and γ tocopherols. α-Tocopherol is a synthetic form of vitamin E containing several isomers. In humans, vitamin E is distributed exclusively in the cellular membranes, fat cells and lipoproteins. Vitamin E is localized primarily in the mitochondrial, microsomal, and synaptosomal subcellular fractions of the brain. Dietary vitamin E is usually in the form of α- and γ-tocopherol, and 20–40% of this is normally absorbed from the intestine. Absorption of vitamin E depends on the individual's ability to absorb fat.

Vitamin E serves as a free radical scavenger[21]. It is a component of antioxidant systems that detoxify the reactive oxygen species and prevents oxidative injury to the polyunsaturated fatty acids, cell membranes, cytoskeleton and nucleic acids.

Reasoning that free radical scavengers may slow down the progression of Parkinson's disease[22], the DATATOP (Deprenyl And Tocopherol Antioxidative Therapy Of Parkinsonism) clinical trial was initiated in 1987 to examine the benefits of deprenyl (selegiline) and α-tocopherol in slowing the progression of Parkinson's disease[23,24].

DATATOP was a double-blind, multicenter, placebo-controlled clinical trial aimed at slowing the decline of patients with early Parkinson's disease. The specific aim was to determine whether or not chronic administration of deprenyl 10 mg/day and/or

tocopherol 2000 IU/day to patients with early, untreated Parkinson's disease prolonged the time until levodopa therapy was needed to treat emerging disability. Deprenyl and tocopherol exert antioxidant effects through separate but complementary mechanisms of action. The 34 participating centers in the DATATOP trial enrolled 800 patients with early, otherwise untreated Parkinson's disease. The patients were randomized to one of the following four groups based on the 2×2 factorial design of the study: deprenyl and tocopherol placebo; deprenyl placebo and tocopherol; deprenyl and tocopherol; deprenyl placebo and tocopherol placebo. After 14±6 (mean±SD) months of controlled observation, deprenyl 10 mg/day was found to delay the time significantly until enough disability developed to warrant the initiation of levodopa therapy. This effect was largely sustained during the 8.2 years of observation, including open-label deprenyl treatment and a second treatment randomization to continue deprenyl or switch to placebo[25]. There were no accompanying benefits of deprenyl in postponing levodoparelated adverse effects or extending life. The issue of whether deprenyl delayed clinical decline because of an effect on underlying disease progression or because of mild dopaminergic activity from the drug or its metabolites was not settled by this study. Unfortunately, α-tocopherol produced no benefits in these patients.

## DIETARY VITAMIN E AND VITAMIN E SUPPLEMENT

Oxidative stress may contribute to neuronal degeneration in Parkinson's disease[9]. Several vitamins, such as vitamins E and C, and carotenoids can protect cells from oxidative damage[26] and could potentially reduce the risk of Parkinson's disease. Zhang and colleagues[27], therefore, conducted a study to examine prospectively the associations between intakes of vitamin E, vitamin C, carotenoids and vitamin supplements and risk of Parkinson's disease in two large cohorts: the Nurses' Health Study (NHS) and the Health Professionals Follow-Up Study (HPFS). The advantage of using these two cohorts was the availability of repeated and validated dietary assessments, including detailed information on dosage and duration of use of antioxidant vitamin supplements.

In 1976, 121700 female US registered nurses aged 30–55 years completed a mailed questionnaire about their medical history and health-related behaviors. These participants formed the NHS cohort. In 1986, 51529 male US health professionals (dentists, optometrists, osteopaths, podiatrists, pharmacists and veterinarians) aged 40–75 years answered a similar mailed questionnaire and formed the HPFS cohort. Every 2 years, participants filled out questionnaires to update information on potential risk factors and to ascertain newly diagnosed diseases. The questionnaires collected dietary information every 4 years from 1980 to 1994 in the NHS, and from 1986 to 1994 in the HPFS. Subjects who were diagnosed with Parkinson's disease, stroke, or cancer were excluded from the study. A total of 76890 women and 47331 men were included for the analyses.

Each subject specified how many portions they consumed of each food and how often on average over the previous year they had consumed that amount of each food. They also specified their daily dosage of vitamin E supplements and vitamin C supplements as well as weekly number of multivitamins taken.

New cases of Parkinson's disease were identified by self-report on the biennial questionnaires, and then validated by the investigators by writing to the physician

indicated by the participant as his or her primary neurologist. A total of 371 new cases of Parkinson's disease were documented (161 in women and 210 in men).

The investigators calculated person-years of observation for each participant from the date of returning the dietary questionnaire to the date of diagnosis of Parkinson's disease, death, or end of follow-up, whichever came first. Men and women were categorized by quintiles of their baseline intake of vitamin E, vitamin C and carotenoids for nutrient analyses. The incidence rate was calculated by dividing the number of Parkinson's disease cases by the number of person-years of follow-up for each category of nutrient intake. Relative Risks (RR) was calculated by dividing the incidence rate in an exposure category by the corresponding rate in the reference category. Age-adjusted RR were also calculated.

Of every ten subjects, about four were found to use multivitamins, three used vitamin C and two used vitamin E. Neither intake of total vitamins E or C or use of vitamin E or vitamin C supplements or multivitamins was significantly associated with risk of Parkinson's disease. The risk of Parkinson's disease, however, was significantly reduced among men and women with high intake of dietary vitamin E (from foods only). Consumption of nuts was also significantly associated with a reduced risk of Parkinson's disease. Intake of dietary vitamin C and carotenoids did not appear to reduce the Parkinson's disease risk.

Because smoking was strongly associated with a lower risk of Parkinson's disease in these two cohorts[28], the investigators also examined the association between dietary vitamin E intake and risk of Parkinson's disease according to smoking status, to minimize residual confounding by smoking. Baseline intake of dietary vitamin E reduced the risk of Parkinson's disease among both non-smokers and smokers in women, and only among smokers in men.

The investigators concluded that the use of vitamin supplements (including vitamin E) and

**Table 1** Foods rich in vitamin E

| *Foods* | *Vitamin E (mg/serving size)* | *Vitamin E (mg/100g food)* |
|---|---|---|
| Sunflower seeds | 14.3 (1 ounce dry roasted) | 50.27 |
| Almonds | 6.7 (1 ounce dried) | 26.18 |
| Canola oil | 2.9 (1 tablespoon) | 20.95 |
| Wheat germ | 4.0 (1 ounce toasted) | 18.14 |
| Hazelnuts | 6.8 (1 ounce dry roasted) | 15.19 |
| Olive oil | 1.7 (1 tablespoon) | 12.4 |
| Peanut butter | 3.2 (2 tablespoons) | 10 |
| Turnip greens | 1.6 (1 cup cooked) | 2.92 |
| Mustard greens | 2.8 (1 cup cooked) | 2.01 |
| Soybeans | 3.4 (1 cup cooked) | 1.95 |
| Broccoli | 2.6 (1 cup cooked) | 1.65 |

| | | |
|---|---|---|
| Avocado | 2.3 (1 medium) | 1.34 |
| Spinach | 1.6 (1 cup raw) | 1.3 |
| Spaghetti sauce | 3.1 (1 cup cooked) | 1.25 |
| Mango | 2.3 (1 medium) | 1.12 |
| Pinto beans | 1.6 (2 tablespoons) | 0.94 |
| Brussels sprouts | 1.3 (1 cup cooked) | 0.58 |

Information gathered from www.cancerproject.org/medicine/e.html, www.feinberg.northwestern.edu.nutrition/factsheets/vitamine.pdf, and www.cc.nih.gov/cc/supplements/vite

high intake of carotenoids did not appear to reduce the risk of Parkinson's disease. The reduction in risk associated with high dietary vitamin E intake, but not vitamin E supplement, suggests that other constituents of foods rich in vitamin E or lifestyle factors related to dietary vitamin E intake, rather than vitamin E itself, may be protective. It is well known that more than 50% of dopamine neurons are lost by the time the Parkinson's symptoms become clinically manifest[29]. Therefore, Parkinson's disease may be related to a long-term or remote pathological insult. The investigators therefore emphasized that they could not exclude the possibility that the conflicting results between vitamin E intake from foods and from supplements reflected the importance of vitamin E intake earlier in life, as dietary intake may have been consistent over long periods, whereas widespread use of vitamin E supplements was relatively recent.

This observation that foods rich in vitamin E may prevent Parkinson's disease is preliminary. We need future studies to confirm and explain it. However, it does not cost extra for us to consume foods that are rich in vitamin E. The amounts of vitamin E in milligrams per serving and per 100mg food are listed in Table 1.

## HIGH-DOSE COENZYME Q10

Coenzyme Q10 is the electron acceptor for complexes I and II and also a potent antioxidant. The function of complexes I and II/III in the mitochondrial electron transport chain is impaired in Parkinson's disease. Inhibition of complex I by 1-methyl-4-phenyl-1,2,3,6-tetra-hydropyridine (MPTP) can cause human parkinsonism[30]. Complex I activity in the postmortem substantia nigra in patients with Parkinson's disease was shown to be decreased[31]. It was later discovered that complex I activity in platelets from patients with Parkinson's disease was also decreased[32]. The levels of coenzyme Q10 in the platelet mitochondria of patients with Parkinson's disease were reduced[33] and the serum level of coenzyme Q10 in patients with parkinsonism was significantly lower than that in age-comparable patients with stroke[34]. Oral supplementation with coenzyme Q10 reduced the loss of dopamine and dopaminergic axons in the striatum in 1-year-old mice treated with MPTP[35]. Oral supplementation with coenzyme Q10 in rats resulted in significant increases in the concentration of coenzyme Q10 in mitochondria in the cerebral cortex[36]. In a pilot study, Shults and colleagues[37] demonstrated that oral coenzyme Q10 was well

tolerated and resulted in significant elevations of plasma levels of coenzyme Q10 in Parkinson's disease patients.

Based on the above data, Shults and coworkers and the Parkinson Study Group[38] conducted a dose-ranging study to evaluate the safety and tolerability of high doses of coenzyme Q10 and the ability of coenzyme Q10 to reduce the rate of functional decline in patients with early Parkinson's disease. Eighty subjects with early Parkinson's disease, who did not require treatment for their disability, participated in this multicenter, randomized, parallel-group, placebo-controlled, doubleblind, dose-ranging trial. Subjects were randomly assigned to placebo or coenzyme Q10 at dosages of 300, 600, or 1200mg/day. Every subject, regardless of group to which they were assigned, also received 1200 IU of vitamin E per day. The subjects underwent evaluation with united Parkinson Disease Rating Scale (UPDRS) at the screening, baseline, and 1-, 4-, 8-, 12- and 16-month visits. They were followed up for 16 months or until disability had developed requiring treatment with levodopa. The primary response variable was the change in the total score on the UPDRS from baseline to the last visit.

At the baseline visit, the groups were well matched for sex, age, severity of Parkinson's disease (UPDRS and Hoehn and Yahr scale scores), disability (the Schwab and England Scale score) and intellectual function (the Mini-Mental State Examination score). Coenzyme Q10 was well tolerated in all of the treatment groups. No dosage reductions were required. No clinically significant laboratory abnormality was found. All groups receiving Q10 had highly significant increases in the mean plasma level of coenzyme Q10 from baseline to the last visit. Treatment with coenzyme Q10 also increased the activity of the electron transport chain from NADH to cytochrome C reductase (complexes I and III), which depends on endogenous coenzyme Q10. The adjusted mean total UPDRS changes (the difference between the last and the baseline visit; positive values indicating worsening) were +11.99 for the placebo group, +8.81 for the 300-mg/day group, +10.82 for the 600mg/day group, and +6.69 for the 1200-mg/day group. The *p* value for the primary analysis, a test for a linear trend between the dosage and the mean change in the total UPDRS score, was 0.09, suggesting a positive trend for the trial. Secondary analysis showed that the difference between the 1200-mg/day and placebo groups was significant ($p$=0.04). This pattern was the result of similar changes in the mental, activities of daily living (ADL) and motor subscores of the UPDRS (Figure 1).

They concluded that coenzyme Q10 was safe and well-tolerated at dosages of up to 1200 mg/ day. Less disability developed in subjects assigned to coenzyme Q10 than in those assigned to placebo, with greatest benefits observed in subjects receiving the highest dosage. Coenzyme Q10 appears to slow the progressive deterioration of function in Parkinson's disease. The investigators suggested that their data were consistent with the hypothesis that mitochondrial dysfunction plays a role in the pathogenesis of Parkinson's disease and that treatments targeted at mitochondria might ameliorate the functional decline in Parkinson's disease.

As expected, this study has generated a great deal of excitement in Parkinson's disease patients. The author has received numerous phonecalls from our Parkinson's disease patients who wish to be started on coenzyme Q10. Should every Parkinson's disease subject be on coenzyme Q10? 'Not just yet', according to Dr Shults, the leading author of the study[39]. Dr Shultz emphasized that the findings were preliminary and that the Parkinson Study Group hopes to seek funding for a larger study with 400 patients. He recommended against endorsing coenzyme Q10 as a therapy because it is not regulated by the Food and Drug

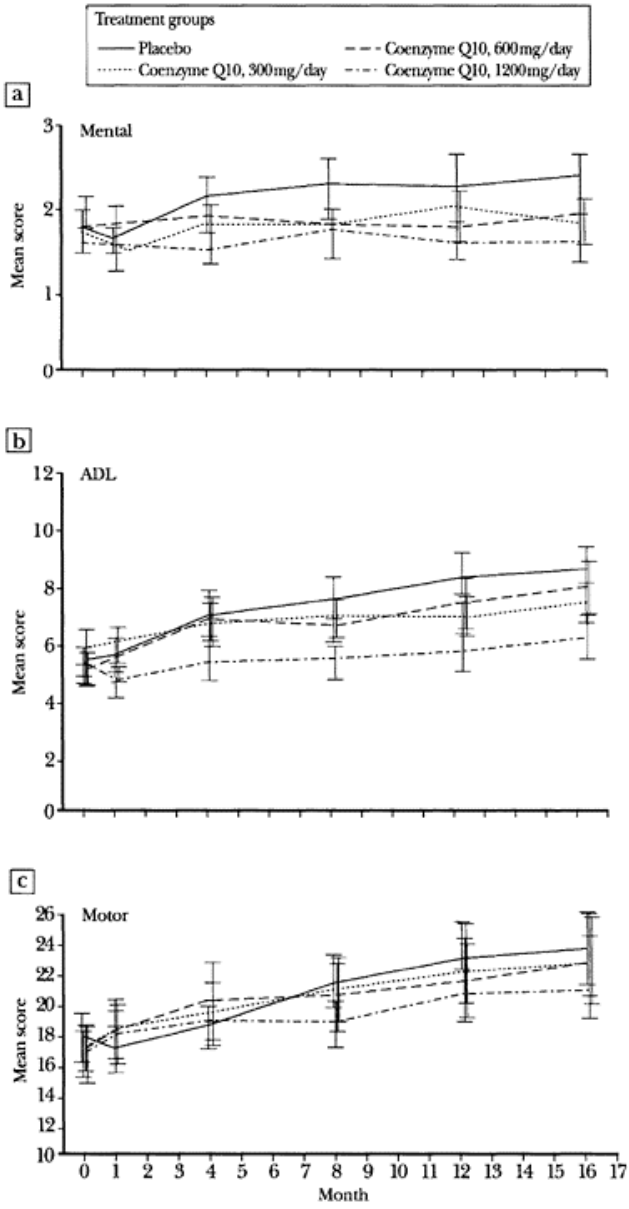


**Figure 1** The three parts of the Unified Parkinson's Disease Rating Scale (UPDRS). The pattern of attenuation of the worsening of the total UPDRS score by coenzyme Q10 was also seen

in each of the three parts of the UPDRS (mental; activities of daily living (ADL) and motor, last observation carried forward). (From reference 38)

Administration and there is no way to guarantee the purity of over-the-counter coenzyme Q10 supplement[39].

## LIPOIC ACID

Fatigue is one of the most common complaints from Parkinson's disease patients. Using the Multidimensional Fatigue Inventory (MFI)[40] measuring five dimensions of fatigue independently (general fatigue, physical fatigue, reduced motivation, reduced activity and mental fatigue), we[7] have shown that Parkinson's disease patients report increased physical fatigue and mental fatigue compared to normal subjects.

Lipoic acid is an antioxidant commonly used as a dietary supplement in the USA. Users believe that lipoic acid may slow down the aging process, improve memory and lower blood sugar. A website that sells diet supplements through the Internet, http://www.iherb.com/, claims that lipoic acid is one of the best-selling antioxidants. It costs about US$50–100/month. It is crucial for us to investigate the effectiveness of lipoic acid to justify the costs.

Our daily diet contains lipoic acid. Foods derived from tissues with a high metabolic activity, such as muscle, have a high lipoic acid content. In addition, lipoic acid can be obtained by *de novo* biosynthesis from fatty acids and cysteine[41]. From food or biosynthesis, only trace amounts of free lipoic acid are absorbed. A much higher concentration of lipoic acid is obtained after oral intake of therapeutic doses (up to 1800 mg/day).

Oral supplement of lipoic acid strengthens tissue antioxidant capability[42] and may be effective in reducing physical fatigue and mental fatigue. Khanna and associates[43] found that a lipoic acid supplement protected against oxidative lipid damage induced by exercise in the heart, liver and muscles[43]. Stoll and colleagues[44] demonstrated that lipoic acid improved the performance of aged mice in three frontallobe-related cognitive tests including habituation in the open field, Morris water maze and active avoidance learning.

We have conducted a double-blind, placebocontrolled trial to investigate whether lipoic acid is effective in reducing physical fatigue and mental fatigue in Parkinson's disease (publication in preparation). We assigned 15 Parkinson's disease subjects randomly to the treatment group (six, mean age 65.3±7.1) or placebo group (nine, mean age 59.8±11.2). The disease severity was not different between the two groups. Each subject took lipoic acid 600 mg three times a day or placebo for 12 weeks. The primary outcome measure included the MFI, which measured five dimensions of fatigue (general fatigue, physical fatigue, mental fatigue, reduced motivation and reduced activity) and finger tapping. The secondary outcome measures included the Center of Epidemiological Study—Depression Scale (CES-D), the Epworth Sleepiness Scale (ESS), Tower of

London (TOL) and Paced Auditory Serial Addition Task (PASAT). We found that the effects of lipoic acid were not different from those of placebo on the scores of physical fatigue (before and after lipoic acid, 10.2±4.6 vs. 12.2±5.7; placebo 9.7±4.4 vs. 12.6±5.1) or mental fatigue (before and after lipoic acid 13.7±2.6 vs. 13.2±2.5; placebo 10.4±3.4 vs 10.9±4.2) in the MFI and other secondary outcome measures. We therefore concluded that lipoic acid, at a dose of 1800 mg/day, did not improve physical fatigue or mental fatigue in Parkinson's disease subjects.

## CONCLUSIONS

The use of CAM is common in Parkinson's disease subjects. A few evidence-based studies have investigated the effectiveness of these therapies. These studies demonstrated that:

(1) Vitamin E supplement did not slow down the progression of mild Parkinson's disease.
(2) Dietary vitamin E, but not vitamin E supplement, was associated with a reduced risk for Parkinson's disease.
(3) High-dose coenzyme Q10 may slow down the progression of early Parkinson's disease.
(4) A small, controlled study demonstrated that lipoic acid was not effective in reducing fatigue in Parkinson's disease subjects.

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# 20
# Peripheral neuropathy

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*Complementary Therapies in Neurology: An Evidence-Based Approach*
Edited by Barry S.Oken
ISBN 1-84214-200-3 

Peripheral neuropathy is a common disorder with many manifestations and many etiologies, with a prevalence of about 2% increasing with age up to about 8%[1,2]. Individual nerves may be affected, as in carpal tunnel syndrome, or multiple nerves may be affected, as in diabetic polyneuropathy. Peripheral neuropathies may predominantly affect small nerve fibers or large fibers, and be predominantly demyelinating or axonal. Common symptoms for peripheral neuropathy are weakness and altered sensation, including painful sensations. This chapter is organized by underlying etiology because the diverse causes of peripheral neuropathy often have no similarity, for example carpal tunnel syndrome related to repetitive motion injury and toxic neuropathy secondary to cisplatin. Review of the literature for this chapter was generally limited to controlled peripheral neuropathy clinical trials published in English.

Some neuropathies are caused by overt vitamin deficiencies such as of vitamin $B_{12}$ and folate. In these cases supplementation would obviously benefit the patient, but these therapies for overt vitamin deficiencies will not be discussed. Vitamin supplementation is often given to patients with peripheral neuropathy of uncertain etiology even though it is of unclear utility. Generally, administration of vitamins has no associated problems, but high doses of certain vitamins, $B_6$ in particular, can by itself cause a peripheral neuropathy. Doses of vitamin $B_6$ above 100 mg/day should not be used[3].

## DIABETIC NEUROPATHY

Diabetes is associated with a variety of neuropathies including mononeuropathies and lumbosacral radiculoplexus neuropathy (sometimes inaccurately referred to as diabetic amyotrophy)[4,5]. Clinical trials of complementary and alternative medicine (CAM) therapies have been limited to diabetic polyneuropathy, a distal symmetric sensorimotor polyneuropathy that is the most common neuropathy associated with diabetes. There has been one review of botanicals and other dietary supplements in diabetic neuropathy[6].

### α-Lipoic acid

α-Lipoic acid (ALA) is an antioxidant and a required co-factor for mitochondrial enzymes that can be obtained from the diet or from biosynthesis. ALA has been the most studied CAM therapy for diabetic neuropathy.

Ziegler and colleagues initiated a series of controlled clinical trials with a 3-week trial involving 328 non-insulin-dependent diabetics with symptomatic peripheral polyneuropathy[7]. Patients were randomly assigned to receive intravenous placebo or 100, 600 or 1200 mg of ALA for 14 days out of 3 weeks. The primary outcome measure was the Total Symptom Scale (TSS) that was generated from neuropathic symptoms: pain, burning, paresthesia and numbness. Secondary outcome measures included the Neuropathy Symptom Score, the Neuropathy Disability Score that is based on semi-quantitative neurological examination and a self-rated pain scale. ALA doses of 600 mg and 1200 mg produced significant improvements compared to placebo in TSS, Neuropathy Disability Score and the pain scale. Notably, 1200mg intravenous ALA was associated with a low incidence of nausea and vomiting. A follow-up trial by the same group involved 510 diabetics treated with diet, oral antidiabetic medications or insulin, and with stable glycemic control[8]. Patients were randomized to one of three groups: 3 weeks of intravenous 600 mg ALA followed by 600 mg orally for 6 months; 3 weeks of intravenous 600 mg ALA followed by oral placebo for 6 months; or intravenous placebo for 3 weeks followed by oral placebo for 6 months. There was no significant difference in the TSS in the treated compared to placebo groups. There was benefit from the ALA on the Neuropathy Impairment Score, a semi-quantitative neurological examination of strength, sensation and reflexes after 3 weeks, and a trend towards improvement after 7 months ($p$=0.09). There were no significant side-effects from ALA intravenously or orally. A small trial of oral ALA, 600 mg three times per day for 3 weeks, found significant improvement in TSS and Neuropathy Disability Score compared to placebo treatment[9]. There were no significant adverse events with this high ALA dose. A recent trial from Ziegler's group evaluated the effects of 600 mg ALA infused daily, 5 days per week for 14 infusions in 120 patients with diabetic sensorimotor polyneuropathy[10]. The TSS improved in the treated compared to the control group (Figure 1). Improvements were also noted on the Neuropathy Impairment Score, neuropathic symptoms of lower limbs and global assessment of efficacy by both the physicians and the patients. Nerve conduction studies showed improvements in distal latency of the sural nerve. There was no improvement in other nerve conduction measures, quantitative sensory testing or autonomic function measures (heart rate changes with deep breathing).

Another trial evaluated long-term oral ALA in 65 patients with symptomatic mild diabetic polyneuropathy randomized to receive ALA 600mg/day, ALA 1200mg/day or placebo for 24 months[11]. There was significant improvement in the ALA groups compared to the placebo control at outcome based on nerve conduction studies. These positive outcome measures included sural sensory nerve conduction velocity, sural sensory nerve action potential amplitude and tibial motor nerve conduction velocity. There was no improvement in the tibial motor distal latency. There were also no differences between the groups on the Neuropathy Disability Scale.

One clinical trial in 73 diabetic patients with objective evidence of cardiac autonomic neuropathy reported beneficial effects of a 4-month trial of 800 mg oral ALA. The measures of cardiac autonomic neuropathy were heart rate variability assessed from a 5-min electroencephalogram (EGG) recording in the supine position with normal breathing[12]. The improvement was seen in the root mean square successive difference and in the spectral power in the low-frequency band (0.05–0.15 Hz). There was a trend

towards improvement in the high-frequency band but no difference in cardiac autonomic symptoms.

It is reasonably established that a short course of intravenous ALA improves some symptoms and signs of diabetic polyneuropathy. There are very suggestive but less definitive data concerning the utility of longer-term oral ALA. This may in part be related to the relatively poor gastrointestinal absorption of ALA, but may simply reflect fewer large clinical trials.

### γ-Linolenic acid

γ-Linolenic acid (GLA) is an ω-6 fatty acid that is usually synthesized *in vivo* from linoleic acid.

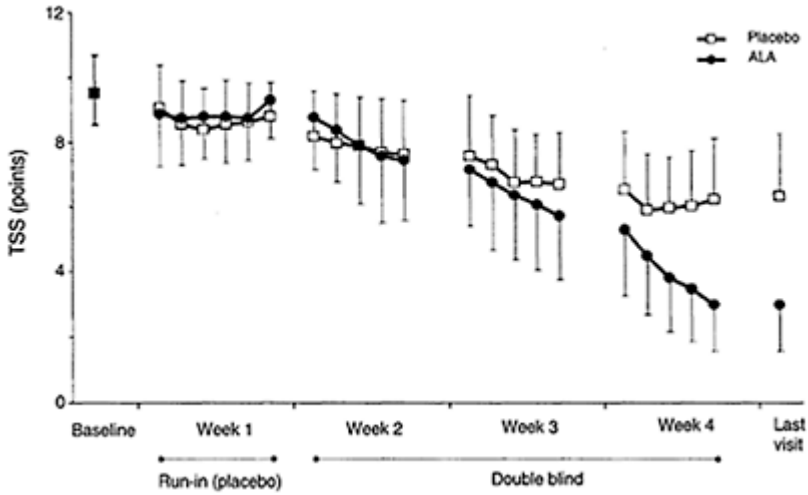


**Figure 1** The beneficial effect of intravenous α-lipoic acid (ALA) 600 mg/day compared with placebo for 3 weeks (14 treatment days) on the Total Symptom Score (TSS) in 120 patients (60 per group) with diabetic polyneuropathy. Values are mean and 1 SD

In diabetes, this metabolic conversion is impaired and thus GLA may become an essential fatty acid. There have been two trials of GLA in diabetic neuropathy. In a pilot trial, 22 patients with distal diabetic neuropathy were given a daily dose of 360 mg GLA as a constituent of evening primrose oil or placebo[13]. After 6 months the treated group was better than the placebo group on symptom scores and nerve conduction studies (median, peroneal and sural). There was a follow-up multicenter placebo-controlled trial of 111

patients with mild diabetic polyneuropathy treated with a slightly higher dose of GLA, 480mg/day (12 capsules of 40 mg each per day)[14]. The capsules used were EF4, a variety of evening primrose oil that contains linoleic acid in addition to GLA. For 13 of the 16 outcome measures, including nerve conduction studies (median, peroneal and sural), quantitative sensory testing and semi-quantitative neurological examination, the GLA group did better than the control group. There were no obvious differences in glycemic control between the groups, and the treatment was well tolerated without any differences in side-effects between the groups.

## Myoinositol

There are some older findings suggesting that myoinositol was decreased in diabetic nerves. As a result, there were a series of small clinical trials evaluating the utility of oral supplementation of myoinositol in diabetic neuro- pathy, but there was no beneficial effect[15–17]. A later study that analyzed sural nerves in controls and diabetics found no evidence of myoinositol deficiency as part of the pathogenesis of diabetic neuropathy[18].

## Magnetic therapy

Static magnetic field therapy has been evaluated in two trials. The first trial evaluated 24 subjects with painful peripheral polyneuropathy, about half secondary to diabetes[19]. Subjects were assigned to wear magnetic foot insoles for 4 months (most were unilateral for 1 month, switched to the other foot for 1 month and then both feet for 2 months). There was improvement in neuropathic symptoms of burning pain and numbness and tingling in the diabetic cohort but there was no change in the non-diabetic cohort. There was also no change in the electrophysiological measurements. The follow-up study was a multicenter trial of 375 patients with diabetic peripheral neuropathy[20]. Subjects were assigned to wear magnetized insoles constantly for 4 months or a similar unmagnetized device. Outcome measures were visual analog scale for numbness or tingling, visual analog scale for burning, quality of life (exercise-induced foot pain and sleep interruption secondary to pain), nerve conduction studies and quantitative sensory testing. There were statistically significant differences between the groups in burning, numbness or tingling and for exercise-induced foot pain. There were no differences in nerve conduction studies or quantitative sensory testing.

## Other

A small randomized double-blind trial of 21 diabetics using vitamin E 900 mg/day for 6 months demonstrated improvement in some of the nerve conduction study electrophysiological parameters compared to the placebo group, despite there being no difference in glycemic indexes[21]. There were no beneficial effects of pyridoxine in several small controlled trials in patients with diabetic neuropathy[22–24]. Acrossover trial of 20 diabetic subjects evaluated acetyl-L-carnitine, administered intramuscularly 500 mg twice per day for 15 days[25]. There was a significant benefit on the visual analog pain scale following treatment compared to placebo in this single-blind experiment, but there was no effect on

vibration perception threshold. There have been no controlled trials for acupuncture, although there have been uncontrolled trials[26].

## CARPAL TUNNEL SYNDROME

Carpal tunnel syndrome is the most common nerve entrapment syndrome. Conventional treatment has included wrist splints, injections, anti-inflammatories, physical therapy and lifestyle changes that decrease the movements that may precipitate the injury. There have been systematic reviews of all treatments for carpal tunnel syndrome that include CAM therapies[27,28].

### Vitamin $B_6$

There have been several small controlled trials of vitamin $B_6$ (pyridoxine) for carpal tunnel syndrome with inconsistent results. Three of the trials contained fewer than 20 subjects[29–31] and the best-designed trial contained 35 subjects. This latter trial showed no significant benefit in electrophysiological signs, clinical signs or significant symptoms from 200 mg of pyridoxine per day for 12 weeks[32].

### Yoga

There was a randomized trial of Hatha yoga (Iyengar style) consisting of 42 subjects with carpal tunnel syndrome[33]. The yoga group met twice weekly for 8 weeks and the yoga poses focused on the upper body. The control group was offered a wrist splint and could be considered a current treatment group. Following the intervention, the yoga group was better than the control group as assessed by grip strength, pain and Phalen sign but there was no difference between groups in sleep disturbance, Tinel sign and median nerve motor and sensory conduction time. There were some limitations to the study including sample size, the inconsistent use of an optimal splint in the con- trol group and the analysis technique[34–37]. Pending further study the results are promising preliminary findings.

### Chiropractic

Chiropractic manipulation was evaluated in a randomized, controlled trial of 91 patients with carpal tunnel syndrome[38]. The chiropractic group received manipulation of the soft tissues and bony joints of the upper extremities and spine with a decreasing frequency over 9 weeks, ultrasound over the carpal tunnel and nocturnal wrist supports. The control group received standard medical care including ibuprofen as well as nocturnal wrist supports. Outcome measures included pre- and postassessments of self-reported physical and mental distress, nerve conduction studies and vibrometry. There was significant improvement in both groups in terms of perceived comfort and function, nerve conduction values and finger sensation. However, there were no significant differences between the groups, making it unclear whether either intervention was better than the

findings in an untreated natural history control group. The manipulation group reported fewer complications than those receiving ibuprofen.

### Other

There has been one controlled trial of low-level laser stimulation on acupuncture points in carpal tunnel syndrome[39] following up on two uncontrolled trials[40,41]. Eleven patients were evaluated with a crossover design trial using two series of 9–12 treatments consisting of microampere-level stimulation as well as laser application to acupuncture sites on the skin lasting 3–4 weeks for each series. There were significant decreases in self-rated pain, median sensory nerve conduction latency, and Phalen and Tinel signs after the real treatment series but not after the sham treatment series. A double-blind placebo-controlled evaluation of magnets applied to the wrist for 45 min in 30 patients with carpal tunnel syndrome revealed no beneficial effects on pain symptoms assessed acutely and at 2-week follow-up compared to control therapy[42].

## HUMAN IMMUNODEFICIENCY VIRUS NEUROPATHY

Peripheral neuropathy is a common and problematic complication of HIV disease and has several causes. Although use of complementary therapies such as massage and acupuncture are common for HIV-related neuropathy[43], there is little evidence to demonstrate their effectiveness. There was a non-controlled trial of electroacupuncture in 11 patients with HIV disease who had antiretroviral drug-induced neuropathy[44]. Based on complete data from seven of these subjects, there were improvements in self-reported measures including feelings of increased physical strength and health-related quality of life. There were several parameters from the nerve conduction studies that also improved, including the maximum H-reflex amplitude. The maximum M-response could not be obtained because pain did not allow patients to tolerate the stimulus intensity needed to elicit the maximum M-response. However, the direct muscle response at the intensity used to elicit the maximum H-reflex also showed an increase in amplitude compared to the pretreatment baseline. A larger, multicenter trial treated 239 patients with HIV-related peripheral neuropathy with a standardized acupuncture regimen or a control acupuncture condition—needles inserted at points not corresponding to any standard acupuncture points[45]. The study lasted 14 weeks and the treatment was twice per week for 6 weeks followed by once a week for 8 weeks. This study had another treatment arm where 136 patients were randomized to amitriptyline 75 mg/day or placebo. There was a significant decrease in pain in all four groups: both treated and both control groups. There was no difference between the standardized acupunc-ture and the control acupuncture groups in the primary outcome measure, which was subjective pain based on daily diary. There was also no difference in a semi-quantitative neurological examination score and a health-related quality of life physical functioning score. There was a statistically significant difference ($p< 0.03$) favoring the standardized acupuncture group in global pain relief at 14 weeks. The investigators minimized this finding by commenting that it was not significant, given the multiple comparisons. However, this finding cannot be minimized too much, because there were several features of the study that may have decreased the

relative effectiveness of acupuncture, including the fact that the treatment acupuncture points used may not be useful[46], the acupuncture treatments did not use electrical stimulation[47] and, as with all acupuncture control groups, acupuncture needle insertions at non-standard acupuncture sites may have beneficial physiological effects.

## OTHER NEUROPATHIES

Cisplatin, an effective anticancer drug, may cause significant neurological toxicity including peripheral sensory polyneuropathy. There was a trial to evaluate whether use of vitamin E may decrease this toxicity; 27 patients receiving cisplatin were randomized to receive vitamin E 300 mg/day or placebo for several days prior to, during and for 3 months following the cisplatin treatment[48]. The vitamin E-treated group had a significantly lower incidence of neurotoxicity. The neurotoxicity score was a combined measure of neuropathic signs and symptoms and electrophysiological changes. The electrophysiological changes were evaluated by sural and median nerve conduction studies. Additionally, the authors performed an animal study that demonstrated no change in effectiveness of cisplatin on tumor growth with the addition of vitamin E.

A crossover trial of 900 mg of St John's wort in 54 patients with painful polyneuropathy of mixed causes found no clear benefit of the treatment on subjective pain ratings and heat and pressure pain thresholds[49]. There was a trend towards an effect on the total pain score but not on any of the subscores. A recent review of painful sensory neuropathy found no evidence for any positive results of CAM therapies for its treatment[50].

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# 21
# Evidence-based complementary and alternative medicine in amyotrophic lateral sclerosis

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*Complementary Therapies in Neurology: An Evidence-Based Approach*
Edited by Barry S.Oken
ISBN 1-84214-200-3 

## AMYOTROPHIC LATERAL SCLEROSIS

Amyotrophic lateral sclerosis (ALS) is a specific form of motor neuron disease in which there are both upper and lower motor neuron signs[1]. The disease is progressive and the prognosis is very poor, with the mean survival being 3–5 years.

'Amyotrophic' refers to muscle atrophy and weakness that is caused by degeneration of lower motor neurons in the brainstem and the spinal cord. 'Lateral sclerosis' refers to the hardening of the lateral columns of the spinal cord caused by degeneration and gliosis of the corticospinal tracts.

Clinically, ALS is characterized by progressive weakness. Typically, the disease spares the sensory system. The region of onset for ALS can be in bulbar, cervical, or lumbar regions. The time course can also vary from a rapid progression with patients becoming ventilator-dependent in a few months, to a slow progression with patients still living independently more than 10 years after diagnosis.

Common clinical presentations of ALS include bulbar, upper motor neuron, and lower motor neuron symptoms and signs:

(1) Bulbar symptoms and signs: dysarthria, dysphagia, sialorrhea (drooling), tongue atrophy and tongue fasciculation;
(2) Upper motor neuron symptoms and signs: hyperreflexia, spasticity, Babinski signs, jaw jerk, snout reflexes, spread of reflexes, incoordination weakness;
(3) Lower motor neuron symptoms and signs: weakness, muscle atrophy and fasciculations.

Familial ALS accounts for about 10% of all patients. It provides us a model to understand the possible pathogenesis of the neuronal death in ALS. Approximately 15% of familial ALS has a Cu/Zn superoxide dismutase gene mutation on chromosome 21[2], and numerous types of SOD1 mutations have been described[3]. Exact mechanisms by which alterations in SOD1 bring about the process of ALS are unknown. One possibility is that these mutations alter the activity of the SOD1 enzyme, and this leads to increased rates of

reactive nitrating species formation[4]. However, it is difficult to attribute the disease solely to the aberrant activity of the SOD1 enzyme[5].

Sporadic ALS accounts for about 90% of the patients. We have a limited understanding of the mechanisms of motor neuron injury and cell loss in sporadic ALS. However, several hypotheses have been proposed:

(1) *Immune or inflammatory mechanisms.* Immune or inflammatory reactions may trigger increased intracellular calcium and motor neuron degeneration[6,7] . Evidence for immune mechanisms include a higher incidence of immune disorders in patients[8], the presence of CD4 and CD8 in the degenerating ventral horn of the spinal cord[9], the presence of paraproteinemias and lymphomas[10] and the presence of within ALS motor neurons[11].

(2) *Free radical-mediated oxidative stress.* Higher levels of protein carbonyl groups and oxidized nucleic acids in brain homogenates from patients with sporadic ALS suggest increased oxidative stress. In addition, fibroblasts from ALS patients with mutant SOD1 appear more sensitive to oxidative stress caused by hydrogen peroxide[12].

(3) *Glutamate excitotoxicity.* Glutamate is a prime candidate as a cause of motor neuron excitotoxicity in ALS, because it is the principal excitatory neurotransmitter in the human motor system, including the corticospinal tract-spinal cord interneurons and cortical association pathways. Additionally, the concentration of glutamate is about 20000-fold higher intracellularly than extracellularly. Tightly regulated energy-dependent systems ensure that extracellular glutamate concentrations remain very low to prevent cell injury. Therefore, disruption of this steep concentration gradient leads to substantial extracellular accumulation of excitatory amino acids[13].

(4) *Neurofilament abnormality.* Neurofilaments are cytoskeletal elements whose normal production and transport to the termini are critical to the health and integrity of motor neurons. The abnormality of neurofilaments may play a role in the pathogenesis of ALS, since neurofilaments accumulate in perikarya and proximal axons in ALS[14]. Pathological features of the disease can be produced in transgenic mice overexpressing various protein filament subunits[15]. In humans, impaired transport of neurofilaments (resulting from a neurofilament gene mutation or an acquired lesion of the neurofilament subunit proteins) may lead to motor neuron degeneration[16].

No effective disease-specific therapies are available for ALS. Based on the hypothesis that excitotoxic damage to motor neurons may play a role in the disease, and observations that inhibited the presynaptic release of glutamate and neuronal damage in a number of experimental models, two clinical trials were carried out using riluzole[17,18]. The results showed that riluzole prolonged survival in patients by 2–3 months. The drug costs about $ 10000 per year in the USA, but many third-party payers cover it. The Food and Drug Administration (FDA) has approved only this drug in the USA for ALS. Because there is no effective treatment for ALS, aggressive symptom management and comprehensive palliative or end-of-life care are essential for patients and their families. The American Academy of Neurology Practice Parameter Subcommittee has recently made evidence-based recommendations for the care of patients with ALS[19].

Progressive and impaired food and fluid intake will develop in ALS patients with bulbar symptoms. This results in malnutrition and weight loss, which further worsens muscle weakness and atrophy in patients. Malnutrition increased the relative risk of death

7.7-fold in patients[20]. Percutaneous endoscopic gastrostomy (PEG) can be placed for patients with ALS who have symptomatic dysphagia, and should be considered soon after symptom onset.

Most ALS patients will eventually develop respiratory insufficiency. Early symptoms of respiratory insufficiency include dyspnea on exertion, marked fatigue, supine dyspnea, disturbed sleep and morning headaches. ALS patients with respiratory insufficiency can use non-invasive positive pressure ventilation to improve their respiratory symptoms, cognitive dysfunction[21], quality of life and survival[22].

## THE USE OF COMPLEMENTARY AND ALTERNATIVE MEDICINE

Probably owing to the lack of effective therapy for ALS, many ALS patients use complementary and alternative medicine (CAM), although they may not tell their physicians.

In Germany, the German Association for Neuromuscular Disease mailed out a questionnaire on CAM to 350 ALS subjects[23]. A total of 171 subjects returned the survey. The use of CAM was reported in 92 (54%) patients. The demographic data were not different between users and non-users. The patients used 73 different methods or substances. Some individuals tried up to 11 different treatments. The most widely used methods were acupuncture (47%), homeopathy (40%), naturopathy (24%) and esoteric treatments (20%). Other treatments used included detoxification, phytotherapy, food supplements, vitamins, traditional Chinese medicine, spiritual practice, magnetic therapy, snake venom, autohemotherapy, ayuvedic medicine, trace elements, diet, Tibetan therapy and fresh-cell therapy. Interestingly, the lower the patients' expectation from CAM, the better was the perceived effect. CAM is most often used in addition to conventional treatments. Patients spend on average $4500 per year on alternative medicine. None of these treatments have been proved to be effective.

In the USA, Carter and Bromberg[24] surveyed 53 ALS patients in the University of Utah Motor Neuron Disease Clinic regarding their use of vitamins, herbal supplements and other compounds. They found that 70% were taking vitamins and 42% were taking herbal supplements. Subjects spent $20–50 per month on herbal medicines and vitamins.

Because the use of alternative medicine is so widespread in patients with ALS, physicians need to become more familiar with alternative medicines and warn their patients of potential complications.

## EFFECTIVENESS OF COMPLEMENARY AND ALTERNATIVE MEDICINE

We have conducted an extensive Medline search using the key words 'Amyotrophic lateral sclerosis' or 'motor neuron disease' crossed referenced with one of the following key words: acupuncture, Alexander technique, alternative medicine, alternative therapy, complementary therapy, chiropractic, EDTA chelating, electromagnetics, electrotherapy, ginkgo, herb, hypnosis, lipoic acid, massage therapy, music therapy, physiotherapy, Qi

Gong, reflexology, Tai Chi, melatonin, meditation, and Yoga. We searched Medline from 1966 to December 2002. The number of CAM therapies that have been used to treat ALS is quite large. However, only a handful of studies have examined the effect of CAM in a well-controlled manner and could validate its effectiveness. Vitamin E, creatine, and acetylcysteine have been used in clinical trials that enrolled more than 50 ALS patients in a randomized, double-blind, controlled fashion.

## Vitamin E

Vitamin E, or tocopherol, is one of the fat-soluble vitamins. Vitamin E includes several structurally related compounds with varying biological activities such as α, β, δ, and γ-tocopherols. α-Tocopherol is a synthetic form of vitamin E containing several isomers. In humans, vitamin E is distributed exclusively in the cellular membranes, fat cells and lipoproteins. Vitamin E is localized primarily in the mitochondrial, microsomal and synaptosomal subcellular fractions of the brain. Dietary vitamin E is usually in the form of α-and γ-tocopherol, and 20–40% of this is normally absorbed from the intestine. Absorption of vitamin E depends on the individual's ability to absorb fat.

Vitamin E serves as a free radical scavenger[25]. It is a component of antioxidant systems that detoxify the reactive oxygen species and prevents oxidant injury to the polyunsaturated fatty acids, cell membranes, cytoskeleton and nucleic acids.

The free radical-mediated oxidative stress hypothesis for the etiology of ALS serves as the theoretical basis for the use of vitamin E for ALS. In 1987, Norris and Denys described a trend towards a lessening of fatigue, fasciculations, and cramps in a small number of ALS patients in an open study[26].

The ALS riluzole-tocopherol study group recently conducted a double-blind, placebocontrolled randomized clinical trial of vitamin E in ALS patients[27]. They enrolled 289 ALS patients who were on riluzole and had disease duration of less than 5 years. They were randomly assigned to vitamin E (500 mg twice a day) or placebo for 1 year. The primary efficacy outcome was determined by measuring the change in functional status using the modified Norris scale[28]. The second outcome measures were the same as those used in the riluzole clinical trial including survival, bulbar function and manual muscle testing. They also measured forced vital capacity and quality of life. The ALS health state scale was divided into four clinical stages (mild, moderate, severe and terminal) was also used[29]. The investigators assessed the patients at the baseline and every 3 months throughout the trial. The investigators found that vitamin E did not appear to affect the survival and motor function in ALS. However, patients taking riluzole and vitamin E remained longer in the milder states of the ALS Health State scale.

The investigotors also compared the concentrations of biomedical markers of oxidative stress at the baseline and 3 months after the treatment in this study[27]. In those patients treated with vitamin E, the plasma level of vitamin E increased significantly. The concentration of thiobarbituric acid reactive species, an index of the extent of cell membrane lipid peroxidation resulting from free radical damage, decreased significantly. In contrast, the glutathione peroxidase concentration increased. It has been reported that plasma glutathione peroxidase levels are decreased in ALS patients compared to age-matched controls[30]. Most interestingly, it was noted[27] that low glutathione peroxidase activity at the baseline was a negative prognostic factor for survival at 12 months. Given

the fact that treatment with vitamin E restored the anomalies observed in antioxidant mechanisms in ALS (thiobarbituric acid reactive species and glutathione peroxidase) without apparently influencing clinical outcome, the authors questioned the relevance of these abnormalities to the pathogenesis of ALS. It may be that the changes in indicators of oxidative stress are a consequence of disease and not a cause. Alternatively, it may be that oxidative stress participates early in triggering disease, and once the pathological process has been initiated, removing the oxidative stress has no consequence for disease progression. In this context, it is interesting to note that, in the study using SOD transgenic mice, where vitamin E delayed the onset of disease and disease progression, treatment was initiated while the animals were presymptomatic[31].

## Creatine

Creatine is found in meat-containing products and is produced endogenously by the liver, kidneys and pancreas[32]. Within the cell, creatine exists as both free creatine and phosphocreatine. In muscle and brain tissues, phosphocreatine functions as a temporal energy buffer in which adenosine diphosphate (ADP) is rephosphorylated to adenosine triphosphate (ATP) during periods of high energy demand. Oral supplementation of creatine increases muscle and brain phosphocreatine concentration. It may inhibit the activation of the mitochondrial permeability transition and protect against neuronal degeneration in ALS.[33] Controlled studies have shown that creatine supplementation increased lean body mass, high-intensity power output and strength in healthy humans[34].

A trial of creatine in patients with various neuromuscular diseases other than ALS, including mitochondrial cytopathies, neuropathic disorders, dystrophies and congenital myopathies and inflammatory myopathies, showed that creatine increased isometric and isokinetic muscle strength and attenuated muscle fatigue[35].

Studies have demonstrated that creatine is not effective in improving patients' respiratory function[36] or survival[37], despite a pilot study using creatine in patients with ALS that generated promising results[38]. Rosenfeld and colleagues[38] treated 20 ALS patients with creatine in a double-blind, placebo-controlled, randomized pilot study. They showed that patients taking creatine had either a significant improvement in their muscle strength or a significantly more modest decline compared to the patients taking placebo.

Drory and Gross[36] showed that creatine did not produce benefits in respiratory function in ALS patients. They compared the pulmonary functions in 14 ALS patients who took creatine 5 g/day and 13 ALS patients with similar pulmonary function who did not take creatine for 4 months; they did not observe any significant difference between these two groups.

Groeneveld and associates[37] showed that creatine at 10 g/day was not effective in improving survival in ALS in the Netherlands. They enrolled 175 patients with ALS and randomly assigned them to creatine monohydrate 10 g/day or placebo. The primary endpoints were death, persistent assisted ventilation and tracheostomy. The secondary outcomes were isometric arm strength, forced vital capacity and quality of life. They demonstrated that creatine treatment was not better than placebo treatment in any of the primary or secondary measures. They concluded that their data provided no evidence for a beneficial effect of creatine on survival, disease progression or symptoms of ALS.

Two large, multicenter, placebo-controlled trials using creatine for ALS subjects are still underway in the USA.

### Acetylcysteine

Free radicals may play a role in the pathogenesis of ALS. Acetylcysteine is a free radical scavenger and may reduce the damage caused by free radicals. Acetylcysteine is a precursor of glutathione, one of the most important intracellular antioxidant defense systems[39]. It promotes the removal of the hydroxyl radical, hydrogen peroxide and hypochlorous acid[40]. In a pilot study[41], 50mg/kg of subcutaneous acetylcysteine seemed to reduce the rate of disease progression in ALS patients.

Louwerse and colleagues[42] conducted a ranclinical trial to assess the effect of treatment domized, double-blind, placebo-controlled with acetylcysteine on survival and disease progression in 110 ALS patients with ALS. Each patient received acetylcysteine or placebo in a dose of 50 mg/kg per day subcutaneously for 12 months. After 12 months, the rate of survival and rates of disease progression, as expressed by decline in muscle strength, pulmonary function, disability and bulbar function were similar in both groups. They concluded that acetylcysteine did not result in a major increase in 12-month survival or a reduction in disease progression in patients with amyotrophic lateral sclerosis.

## CONCLUSIONS

In conclusion, the use of CAM is common in ALS subjects. Only a few studies have been carried out in a well-controlled fashion. Evidenced-based studies have demonstrated that:

(1) Vitamin E may help ALS subjects to stay in the milder state of disease longer, but does not improve their survival. A largescale controlled study will be difficult to carry out, because most ALS subjects are taking vitamin E already.
(2) Creatine does not improve survival in ALS subjects. Two large controlled trials are underway in the United States.
(3) Acetylcysteine does not improve survival or reduce disease progression in ALS patients.

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# 22
# Complementary and alternative medicine for insomnia

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*Complementary Therapies in Neurology: An Evidence-Based Approach*
Edited by Barry S.Oken
ISBN 1-84214-200-3 

Insomnia is a persistent condition of unsatisfactory quantity and/or quality of sleep including difficulty initiating or maintaining sleep. About one-third of the general population suffers from sleep problems; with increasing age, this figure increases[1]. Many insomniacs self-medicate hypnotic drugs which can lead to a host of problems including adverse effects or dependency. According to a Harvard survey[2], insomnia is among the most frequent reasons for people to try complementary and alternative medicine (CAM). Relaxation therapies and herbal medicines are the most popular CAM therapies for this condition[2]. In this chapter, the evidence is reviwed from controlled clinical trials testing the effectiveness/efficacy of CAM modalities as a treatment for insomnia.

## ACUPUNCTURE/ACUPRESSURE

One randomized controlled trial (RCT) ($n$=40) reported greater objective and subjective sleep improvements with acupuncture than with sham treatment[3], while in a trial where patients chose their treatment, sleep improved with both needle and laser acupuncture, but there were no significant differences compared to a waiting-list control group[4]. Acupressure produced better results than both sham and no treatment in an RCT ($n$=84) of elderly insomniacs[5]. Positive effects of acupressure on sleep were also reported in a very small ($n$=6) sham-controlled crossover RCT with healthy volunteers[6]. More recently Chinese investigators randomized 120 elderly patients suffering from sleep disturbances to receive one of three different therapies[7]. Groups A and B received different forms of acupressure on seven auricular points, while, in group C, such points were magnetically stimulated. Treatment lasted for 3 weeks. The results suggest that group C experienced the most benefit in terms of sleep behavior.

## AROMATHERAPY

An unusual form of aromatherapy was tested in 28 patients with sleep problems[8]. All patients were asked to sleep on herbal pillows filled with hops, lemon balm, lavender and orange flowers. The tests were carried out with controls using similar pillows at a lower 'strength' in a sleep laboratory. Polysomnographic records suggested improvements in non-rapid-eyemovement (REM) sleep and a dose-related effect. These findings require independent replication.

**Table 1** Randomized clinical trials of valerian

| *Reference* | *Design (no. days of valerian)* | *Treatment (daily dose)* | *Outcome measures* | *Main results of valerian over placebo* | *Adverse events (no. of reports)* |
|---|---|---|---|---|---|
| Kamm-Kohl *et al.*[20] | parallel groups (14 consecutive) | (a) Baldrian-Dispert® (3×2 capsules) (b) placebo | questionnaires (Bf-S, NOISE, sleep score) | sleep latency and duration improved in more patients | (a) dizziness (2) (b) dizziness (2) |
| Schulz *et al.*[21] | parallel groups (8 consecutive) | (a) Valdespert® (3×405 mg) (b) placebo | questionnaires (VIS-A, SF-A); polysomnography | increase in slow wave sleep but no differences on other measures | no mention |
| Vorbach *et al.*[22] | parallel groups (28 consecutive) | (a) valerian LI 156 (600 mg) (b) placebo | questionnaires (SRA, SF-B, Bf-S, CGI) | greater improvements on almost all measures | (a) headache (1), morning dizziness (1) (b) tiredness (1), nausea/vomiting (1) |
| Leathwood and Chauffard[23] | repeated measures (4 non-consecutive) | (a) aqueous valerian (450 mg) (b) aqueous valerian (900 mg) (c) placebo | questionnaire; activity meter | sleep latency improved | (a) none (b) hangover (1) (c) none |
| Leathwood *et al.*[24] | repeated measures (3 non-consecutive) | (a) aqueous valerian (2×200 mg) (b) Hova® (2× capsules) (c) placebo | questionnaire | sleep latency and quality improved particularly with poor sleepers | nausea (1) |

| | | | | | |
|---|---|---|---|---|---|
| Leathwood and Chauffard[25] | repeated measures (2 non-consecutive) | (a) aqueous valerian (400 mg) (b) placebo | polysomnography | no significant differences | no mention |
| Gessner and Klasser[26] | repeated measures (2 non-consecutive) | (a) Harmonicum Much® (60 mg) (b) Harmonicum Much ® (120 mg) (c) placebo | polysomnography; questionnaire | decrease in sleep stage 4 but no differences in subjective measures | none |
| Balderer and Borbely[27] | repeated measures (1) | (a) aqueous valerian (900 mg) (b) placebo | polysomnography; questionnaire; activity meter | no significant differences | no mention |
| Balderer and Borbely[27] | repeated measures (1) | (a) aqueous valerian (900 mg) (b) aqueous valerian (450 mg) (c) placebo | questionnaire; activity meter | sleep latency improved | no mention |
| Dorn[28] | parallel groups (28 consecutive) | (a) valerian extract (LI 156) 600 mg (b) 10 mg oxazepam | sleep quality questionnaire | improvements in both groups, no inter-group differences | 11 adverse events in valerian and 14 in oxazepam group |
| Donath *et al.*[29] | cross-over (14 consecutive) | (a) Sedonium® (2×300 mg extract) (b) placebo | sleep efficiency; polysomnography | no effect after single dose, reduction of slow wave sleep latency after repeated doses | 3 adverse effects with valerian, 11 with placebo |

## BIOFEEDBACK

Several controlled trials have found no or only minimal improvement in sleep with biofeedback compared with other interventions, no treatment or sham feedback[9–12]. However, in two RCTs[11,12] positive results were reported in patients for whom the particular form of feedback was appropriate. For example, electroencephalogram (EEG) feedback benefited those with anxiety-related insomnia, and sensorimotor rhythm feedback helped non-anxious insomniacs. These findings collectively imply that

biofeedback is not helpful for insomnia in general, but may be beneficial if tailored for the individual patient.

## EXERCISE

A large body of evidence from healthy volunteers suggests that both acute and chronic exercise can have small to moderate positive effects on sleep duration and quality[13]. In an RCT of elderly individuals ($n$=43) with moderate sleep disturbances, insomnia improved in several sleep parameters after they undertook a structured exercise program, compared with those on a waiting list[14].

## HERBAL MEDICINE

Kava *(Piper methysticum)* was shown to improve subjective and objective measures of sleep after acute administration (300 mg) in 12 healthy volunteers in a placebo-controlled trial[15]. It has not been investigated in insomniacs. Kava has recently been associated with severe liver damage and, as a consequence, has been forbidden in several countries[16].

A systematic review of nine placebo-controlled RCTs of the effects of valerian *(Valeriana officinalis)* on sleep reported some positive findings of acute and cumulative effects in patients with insomnia and healthy volunteers[17]. The total sample size of all trials was only 390. In many cases, the studies were associated with significant methodological limitations. Two further RCTs have emerged recently. One study of 35 patients reported similar results for valerian and oxazepam in improving the sleep quality of insomniacs[18]. A subsequent cross-over RCT of valerian compared with placebo ($n$=16) found no acute effects following a single dose. Improvements after 14 days' administration were limited to slow wave sleep[19]. Table 1 provides a summary of all RCTs of valerian as a treatment of insomnia[20–29]. Positive results also exist from RCTs of preparations combining valerian with other herbs such as hops, kava and lemon balm[30–33].

A special case of insomnia exists during benzodiazepine withdrawal. Preliminary data suggest that, in this situation, valerian intake is associated with subjective improvement of sleep, while objective measurements yield no signs of faster onset of sleep[34].

Yoku-kan-san-ka-chimpi-hange (YKCH) is a herbal mixture from the Japanese Kampo tradition which is used for insomnia. It was tested in a small double-blind, cross-over RCT[35]. The results suggested that YKCH increased sleep efficiency and decreased sleep latency. These data are preliminary in nature and require independent replication.

Numerous Chinese herbal remedies are used for insomnia[36]. Sadly the trial data supporting such treatments are insufficient or non-existent.

## HYPNOTHERAPY

Positive results with hypnosis have been reported in a clinical trial of hypnotherapy versus no treatment with 37 female patients[37]. These data are supported by several other RCTs testing hypnotherapy against other active treatments[38–40]. Taking into account

various methodological limitations of these studies, hypnotherapy appears to have some promise in improving sleep.

### Relaxation

A large number of clinical trials have suggested that relaxation training can improve sleep, but few were controlled studies and even fewer were randomized. One RCT (*n*=22) reported

**Table 2** Double-blind, placebo-controlled, crossover randomised controlled trials of melatonin

| *Reference* | *Sample size* | *Interventions (dosage)* | *Results* | *Comment* |
|---|---|---|---|---|
| Garfinkel *et al.*[48] | 12 | (a) melatonin (2 mg 2h pre-bedtime for 21 days)<br>(b) placebo | (a) superior to (b) on sleep efficiency and time awake after sleep onset, not on sleep latency or total sleep | elderly chronically ill patients all taking sleep medication |
| Haimou *et al.*[49] | 26 | (a) melatonin (2 mg fast-release 2 h pre-bedtime for 7 days)<br>(b) melatonin (2 mg slow release)<br>(c) placebo | (a) superior to (c) in sleep latency. (c) superior to (c) in sleep efficiency and activity | free living and institutionalized elderly insomniacs |
| Garfinkel *et al.*[50] | 21 | (a) melatonin (2 mg 2 h pre-bedtime for 21 days)<br>(b) placebo | (a) superior to (b) on all sleep parameters | elderly insomniacs taking benzodiazepines |

that progressive relaxation training (ten sessions over 2 weeks) was superior to no treatment for alcoholic insomniacs[41], while another (*n*=53) found it as effective as stimulus control[42]. A further RCT (*n*=26) reported that, compared with no-treatment, relaxation and sleep hygiene alone produced better longterm results than when hypnotic drugs were also allowed[43]. Two meta-analyses of non-pharmacological treatments for insomnia have concluded that relaxation techniques are effective therapies[44,45]. However, they both included uncontrolled studies and categorized various therapies under relaxation (e.g. autogenic training, biofeedback, desensitization, meditation) so do not constitute compelling evidence. Furthermore, the size of improvements was quite small, although well maintained over time.

## SUPPLEMENTS

The evidence for the efficacy of melatonin in treating insomnia consists of a number of small placebo-controlled trials including at least five that were randomized. Two had negative results[46,47], while three others reported improvements in several sleep parameters

with 2 mg melatonin taken 2 h before bedtime (Table 2). Positive effects have also been reported with healthy volunteers in controlled studies[51,52]. Some studies have suggested that melatonin supplementation is most effective when natural levels are low, as with the elderly[53,54], but the evidence is contradictory[55,56]. It appears to have good tolerability. The current body of evidence is not conclusive, but strongly suggests that melatonin may have some potential in treating insomnia.

The sleep-promoting effects of vitamin $B_{12}$ have been investigated in an RCT of 50 patients with delayed sleep phase syndrome[57] and a small non-randomized trial of ten shift workers[58]; neither found any superiority of vitamin $B_{12}$ over placebo.

## COMMENT

Not least due to the paucity of rigorous clinical trials, the evidence for the efficacy of any complementary therapy is not convincing. Some of these treatments are promising but there is little indication that any of them can match conventional hypnotic medications (which are, of course, much more thoroughly researched) or indeed 'common sense' multicomponent advice (on behavioral approaches, sleep hygiene, relaxation, a sensible dietary regimen, etc.)[59]. Tolerability for the two most promising medicines, valerian and melatonin, appears to be good. Relaxation techniques and regular physical activity probably convey small to moderate benefits on sleep. Given their harmless nature and the many other health benefits associated with these approaches, relaxation and exercise can be recommended in suitable cases. At present, non-pharmacological approaches to the treatment of insomnia seem under-used, under-researched and under-funded.

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# 23
# Non-prescription treatments for snoring or obstructive sleep apnea

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*Complementary Therapies in Neurology: An Evidence-Based Approach*
Edited by Barry S.Oken
ISBN 1-84214-200-3 

## INTRODUCTION

Snoring, a noise related to vibration of upper airway tissue during sleep, is very common, the prevalence varying upon the population studied and method of snoring measurement. Obstructive sleep apnea (OSA) is characterized by episodes of complete (apnea) or partial (hypopnea) pharyngeal collapse during sleep. OSA is also very common, and, in one large epidemiological study, it was present in 9% of women and 24% of men[1]. OSA has been associated with hypertension and cardiovascular morbidity[2–4], as well asreduced quality of life related to symptoms such as sleepiness. Standard treatments for snoring and OSA, including upper airway surgery, positive airway pressure appliances and dental appliances, have extensive scientific evidence detailing their safety and efficacy. Non-prescription treatments such as weight loss and positional therapy are also effective adjuncts for snoring in some patients, although long-term outcome for OSA is less well known. A variety of nonprescription products are marketed for treatment of snoring, and less frequently OSA, with limited or no scientific evaluation.

While the use of alternative treatments is growing, patients may not be forthcoming as to the use of non-prescription products and therapies. The appeal of such treatments generally relates to their ease of access and perceived safety. By using non-prescription products, patients gain a greater sense of control over their treatment. This also avoids the time and expense associated with consultation of a physician or physician surrogate. Alternative medicine is considered ‘safe and natural’, but this is a dangerous assumption. Several areas of concern are immediately apparent. Substances that have an effect upon a person’s state of health are inherently associated with side-effects. The lack of standardization and review of product preparation is also problematic. It is imperative that medical practitioners recognize the importance of nonprescription treatments. If an alternative therapy is effective, then it is an asset. If an alternative treatment is not effective, or harmful, then it is at best a detriment. The delay imposed by efforts at self-treatment is potentially disastrous. Medical practitioners must recognize the appeal of non-prescription medicine and actively seek information about the use of non-traditional treatments from patients.

## MECHANICAL PRODUCTS

### External nasal dilator strips

External nasal dilator strips mechanically pull the lateral nasal vestibule walls outward by means of two parallel springs enclosed in an adhesive strip, and are marketed as a remedy for snoring. The US Food and Drug Administration (FDA) has approved their use '…to provide temporary relief from transient causes of breathing difficulties resulting form structural abnormalities and/or transient causes of nasal congestion associated with reduced airflow'[5]. Side-effects associated with their use include skin irritation or discomfort. The mechanism of action may be related to changes in nasal geometry and resistance. External nasal dilator strips have been shown to enlarge the total cross-sectional area of the nasal airway in healthy adults by 14.2–25%[6–10], with up to an 8 hour duration found in one study[8]. The effect is most pronounced at the level of the nasal valve, the flow-limiting segment of the nasal airway located between the caudal edge of the upper lateral cartilage, nasal septum and nasal floor. Increases of 16–35% in cross-sectional area in this region have been reported[11–15]. Significant increases in inspiratory nasal flow rates with the strips have also been shown in healthy adults[11,16,17]. Changes in nasal resistance innormal subjects are less well known, however, with significant improvement noted by some investigators[13,14,17,18] but not others[10,19,20.]

Most studies of nasal geometry, flow and resistance have shown marked intersubject variation. One proposed explanation for this variability is individual differences in lateral nasal wall compliance[8]. Ethnic differences may also play a role. Two studies found significant improvement in nasal mean cross-sectional area in African-American and Caucasian subjects, although one study found a greater improvement in Caucasians and the other in African-Americans[6,14]. Reduction in nasal resistance was found in Caucasians but not in African-American subjects[14]. The only report in an Asian population found an increase of 16% in total mean nasal cross-sectional area[9]. Many studies of nasal geometry and airflow changes with external nasal dilator strips have been performed in Caucasian populations, which could increase the likelihood of a positive outcome. In others, the ethnicity of study participants was not given. All of these studies have been performed during wakefulness, and caution is warranted in generalizing improvements in nasal airflow and cross-sectional area during sleep.

External nasal dilator strips have been proposed as a treatment for snoring. Significant reductions in subjective snoring intensity based upon bed-partner ratings were found after 2 weeks of use[21]. In this study, snoring reduction was solely based upon bed-partner reports, which are far less accurate than objective measurements. In contrast, changes in objective snoring measurements have been mixed. One study utilizing polysomnography showed no significant improvement in sleep parameters or snoring index in a series of non-apneic snorers[22]. Non-significant differences were also found in a subgroup of patients with nasal valve anomalies. A larger series of polysomnographically recorded habitual snorers had significant improvement in maximum snoring intensity and snoring index during treatment with external nasal dilator strips[23]. Subgroup analysis found significant reduction in snoring intensity and duration only in nonapneic snorers and mild snorers. The only significant changes in sleep architecture during treatment included an increased latency to stage 2 sleep and decrease in delta and theta power, suggesting

impaired sleep. Nevertheless, subjective ratings of sleep quality improved on treatment nights. Another study suggested that use of the strips might decrease arousal frequency in non-apneic snorers[24].

In the majority of studies, dilator strip use by OSA patients has not been associated with clinically significant improvement. Gosepath and colleagues found a small reduction in apnea-hypopnea index (AHI) from 31.7 to 26.3, which was statistically but not clinically significant[12]. However, only four of 26 patients had a reduction in AHI of <10. These four patients had low pretreatment AHI levels (10.3–16.7). Others found no significant reduction in AHI with external nasal dilator strips[23–25]. Disturbingly, Djupesland and coworkers[25] found a significant increase in AHI with external nasal dilator strips. Patients with more severe pretreatment levels of OSA or less severe pretreatment nasal obstruction had the largest increases in AHI. No significant changes in sleep architecture were found in this series.

Upper airway resistance syndrome (UARS) is characterized by frequent transient electroencephalogram (EEG) arousals from sleep related to increased airway resistance and resulting in excessive sleepiness[26]. The degree of airflow limitation associated with such events is less than with apnea or hypopnea. A randomized, double-blind, controlled study in 18 patients with UARS showed significant improvements in two variables[27]. First, the percentage of stage-1 sleep decreased from 8.6±0.8% on placebo nights to 7.1±0.7% on treatment nights ($p$=0.03). Second, on treatment nights the desaturation time, defined as the percentage of sleep time with $SaO_2$ more than 2% below the mean waking level, decreased from 12.2±2.2% to 9.12±1.3% ($p$=0.04). However, no significant change occurred in total sleep time, other sleep stage amounts, arousal index, AHI or sleepiness as measured by the Multiple Sleep Latency Test.

It cannot be overemphasized that the clinical studies of external nasal dilator strips in snorers with or without OSA should be viewed with caution, given methodological concerns, and that the results from these studies cannot be generalized. Clinical series have included small numbers of subjects, ranging from nine to 35, and frequently lack placebo control. Equally important is the lack of data regarding subject ethnicity, given the ethnic differences previously found in nasal resistance changes associated with external nasal dilator strips. Symptoms of nasal obstruction and signs of nasal pathology are variably present or not mentioned. The etiology of nasal symptoms may have particular significance. Roithmann and associates found a greater reduction in nasal resistance, an increase in nasal mean cross-sectional area and improvement in subjective nasal patency in patients with structural nasal abnormalities versus those with mucosal abnormalities[13]. Additional variables make subgroup analysis difficult, and the differing methodologies prevent direct comparison of study results.

## Internal nasal dilators

Variable designs of internal nasal dilator (IND) exist. One such plastic device is placed into the nose and held stationary by means of end tabs containing knobs that press against the lateral nasal vestibule walls. In a brief report of 16 asymptomatic subjects between 25 and 60 years, mean nasal airflow increased from 0.68 l/s to 0.84 l/s[28]. Statistical analysis was not performed. This same type of device was studied in 17 asymptomatic subjects aged 20 to 24 years before and after nasal inhalation of an α-adrenergic agonist[29]. Nasal

resistance was significantly reduced by 65±16% and 63±18% of baseline after insertion of the dilator and inhalation of nasal decongestant, respectively. However, combined treatment with the internal nasal dilator and decongestant yielded a reduction in nasal resistance to only 31±10% of baseline. Although this was a statistically significant change, it was also significantly less than either treatment alone. Earlier, this same group of investigators reported changes in nasal resistance with this type of internal nasal dilator, the external nasal dilator strips and a topical nasal decongestant in 15 asymptomatic subjects aged 18–45 years[20]. The internal nasal dilator and decongestant significantly and similarly reduced nasal resistance. The decrease in resistance with external nasal dilator strips was not statistically significant.

Another internal nasal dilator design is a flexible looped spring made of biocompatible stainless steel wire that exerts circumferential outward pressure in the nasal vestibules. In a preliminary report of subjects with anterior nasal obstruction, 12 of 15 patients reported subjective improvement in breathing[30]. No objective measurements of nasal patency or airflow were used. Of note, tolerance was poor with one-fifth of participants unwilling or unable to use the device. A brief report by these same investigators noted reduced nasal resistance in most patients without details regarding the magnitude or significance of reduction[31]. In another study primarily comparing external nasal dilator strips and topical nasal decongestion in ten healthy subjects, investigators found that the internal nasal dilators resulted in 24.9% and 29.6% increases in peak inspiratory nasal airflow before and after application of a topical decongestant, respectively[10]. External nasal splinting did not significantly increase peak nasal flow in a constricted or unconstricted state.

Subjects in these studies were reportedly free of upper or lower respiratory complaints, although methods of assessment were not given. The population from which participants were chosen and methods of selection is also not detailed. None of the studies cited disclosed ethnicity of study participants. All studies were performed in wakeful subjects, and improved nasal airflow with the internal nasal dilators may not be generalized to sleep.

All published studies of efficacy in snoring and OSA utilized the plastic internal nasal dilator with end tabs previously described. In an uncontrolled ambulatory study, ten subjects had subjective reduction in bed-partner rating of snoring intensity with use of the internal nasal dilator for five nights[32]. Subjective reduction in snoring was also found in an uncontrolled series of 42 male snorers using the internal nasal dilator for 1 month[33]. This latter series assessed daytime tiredness rated by a visual analog scale of 0–100. The mean baseline score of 58 was reduced to 43. In a small series of Japanese subjects, snoring was reduced in all patients based upon subjective bed-partner reports[34].

Few objective studies of efficacy exist. A nonrandomized, uncontrolled report of ten patients undergoing polysomnography to evaluate snoring showed no significant change in frequency of snoring, apnea severity or oxygen saturation levels with internal nasal dilator use[35]. A randomized, unblinded study of 11 patients, one of whom could not tolerate use of the internal nasal dilator during sleep, used polysomnography with sound level measurement to determine internal nasal dilator efficacy[36]. Mean apnea index was 6.4 (1.3–15) and 18 (1.8–60) with and without the internal nasal dilator, respectively. Other determinants of disordered breathing during sleep, such as hypopnea and respiratory effort-related arousals, were not assessed. No change in sleep architecture was reported, which might suggest that the overall level of sleep disturbance by obstructive

breathing may not improve. A significant reduction in snoring intensity was found in the whole group, but there was no subjective improvement in daytime hypersomnolence after 10 days of home use. None of the subjects in these three series suffered from nasal pathology except for minor nasal septal deviation in some. Another group found a statistically significant reduction in percentage of time with snoring only in stages III and IV of non-rapid eye movement (NREM) sleep in 15 patients without nasal pathology (64±39% vs. 33±43%, $p<0.05$)[37]. Using polysomnography with sound level measurement, patients used an internal nasal dilator after 3 h of baseline recording. Mean AHI, oxygenation and total sleep time were unchanged after dilator insertion, although the number of patients with an AHI of >10 per hour of sleep increased from eight to 11. This study was hampered by the significant differences in percentage of stages III and IV rapid eye movement (REM) sleep before and after dilator insertion. Slow-wave sleep was reduced and REM sleep was increased in the latter portion of the night, as would be expected, and might affect evaluation of the efficacy of the internal nasal dilator.

All of the series reported had a small number of subjects and were not controlled. There was frequently a large degree of overlap between treatment and non-treatment variables. There were a small number of studies utilizing objectively determined snoring intensity. No clinically relevant assessment of internal nasal dilator efficacy in OSA was found. Improvement in nasal resistance, nasal airflow or snoring intensity across ethnic groups and in nasal disease states is unknown and the results of these studies cannot be generalized. Additionally, these improvements have only been shown during wakefulness.

Individual intolerance has been reported in several studies[10,33,34,36]. Displacement during sleep may also be a problem[32,34]. A potential risk, although unreported, of mucosal ulceration and subsequent infection exists.

## PHARMACOLOGICAL PRODUCTS

### Lubricant nasal and oral products

A proliferation of dietary supplements for snoring has occurred recently. One type of product is lubricant sprays designed for use in the nose or throat. These products are advertised as a method for snoring reduction rather than a treatment for OSA or other medical conditions. Ingredients listed include oils, vitamins, polysaccharides and water.

Products are aerosolized or dropped into the upper airway, reportedly reducing snoring by lubrication of upper pharyngeal structures. Advertisements for anti-snoring sprays have been found in newspapers and magazines and through direct email and television.

Efficacy has largely been based on subjective reports of snoring reduction. Subjectively defined response suggests a significant improvement; however, objective documentation of such an effect is lacking. Several manufacturers have shared results of unpublished studies sponsored by them to evaluate individual product efficacy. One manufacturer of an orally applied lubricant reported statistically significant reductions in subjective snoring intensity and duration in 25 patients for 5 days of product use. Objective affirmation of product efficacy was lacking. Another oral spray underwent a multiphase trial of product efficacy and safety. An initial questionnaire to establish

efficacy was used, with 97% of respondents reporting a reduction in snoring. However, only 56 of 100 patients polled responded. After 3 weeks of product use, 100 patients were contacted by phone, none reported adverse reactions. Polysomnography was performed in 20 patients in the last phase. The product was used in the second half of the night, with improvement in snoring measured by sound meter in 97%, as defined by any reduction in average decibel level. However, the data presented in the unpublished report did not include enough detail for scrutiny. Neither study report provided by the manufacturers included complete information regarding methodology or results, to establish product efficacy firmly. Of particular concern are the preliminary findings of a study using an herbal nasal spray. Subjective and objective measurements were followed over a 2-week, randomized study in middle-aged, overweight adults. No significant differences in objectively measured snoring intensity or frequency occurred, yet, subjective patient and bed-partner reports showed a lessening in snoring intensity in 65%. Such results highlight the importance of objectively documented efficacy in such products. The Federal Trade Commission (FTC) issued a consumer alert about such products after settling with one manufacturer over unsubstantiated claims of efficacy[38].

Few published studies exist on the efficacy of soft tissue lubricants in snoring reduction. An intranasal phosphocholinamin preparation, derived from lecithin on a mineral oil fraction, was studied versus tap water placebo to establish whether reduction in airflow turbulence by means of soft tissue lubrication reduced snoring[39]. Using sound meter measurements, the treatment group experienced a 25% reduction in snoring index and 13% reduction in maximal decibel level. The placebo group had 1% and 9% reductions, respectively. Of note is the presence of mild-to-moderate obstructive sleep apnea in both patient groups, yet the AHI after instillation of phosphocholinamin or water was not given. Jokic and co-workers, in a placebo-controlled crossover study of an intranasal soft tissue lubricant (phosphocholinamin) in ten men with mild-to-moderate OSA, showed a clinically non-significant reduction in AHI after treatment[40]. The mean baseline AHI of 17 was reduced to only 14 after phosphocholinamin administration versus the placebo group, which increased to a mean AHI of 24. The reduction in AHI in the treatment group was limited to non-REM sleep. No significant change occurred in sleep quality.

Safety is similarly based largely on unpublished reports. No published reports of adverse effects exist to date. One strong concern arises from the potential delay in diagnosis of OSA, as consumers utilize a ‘quick fix’ rather than seeking medical attention. Consumer testimonials provided by some manufacturers mention the pretreatment presence of witnessed apneic spells during sleep, a significant symptom of OSA. In its recent settlement, the FTC required substantial disclaimers of product ineffectiveness for OSA and listing of OSA symptoms in advertisements[38]. A theoretical adverse reaction to lubricant products is lipoid pneumonia. Aspiration of mineral oil can lead to development of lipoid pneumonia. This potential risk was discussed as a limitation to the long-term use of phosphocholinamin[40]. Lipoid pneumonia has also been reported with olive oil aerosolization in the upper airway, an ingredient listed in some products[41]. It is not known whether this risk extends to other non-mineral oils. Lack of association between anti-snoring aerosols and lipoid pneumonia may reflect non-significant exposure, insidious disease onset or other factors.

### Oral dietary supplements

Ingredients in oral dietary supplements for snoring reduction include various herbs, enzymes and, in at least one instance, melatonin. Efficacy of such products is also primarily based upon subjective reports. A single randomized, placebo controlled study of an oral product containing nux vomica, belladonna, *Ephedra vulgaris*, *Hydrastis canadensis*, kali bichromicum, *Teucrium marum* and histaminum hydrochloricum was found[42]. The treatment group had a 79.5% reduction in subjective snoring reports from the subject and bed-partner, while a 45.6% improvement was noted in the placebo group. This further stresses the potential placebo effect of antisnoring products. An isolated case report in the English language literature was found describing treatment of OSA with *San'o-shashin-to*, a Chinese herbal preparation composed of *Scutellariae* radix, *Coptitis* rhizoma and *Rhei* rhizoma[43]. A 76-year-old, non-obese patient, with a pretreatment AHI of 18.4, was treated for an unspecified duration with various herbal remedies including *San'o-shashin-to*. An AHI of 10.7 was documented by polysomnography approximately 1 month later. No additional information such as sleep staging or body position was noted, nor was statistical analysis performed. Certainly, the clinical significance of this difference is questionable. Additionally, significant night-to-night variability in AHI in OSA patients has been reported[44].

Safety is largely assumed from lack of reported adverse effects. Delay in diagnosis of OSA is a concern for these products as well. The presence of prescription substances in herbal products has been documented, although not specifically in anti-snoring preparations[45]. Some enzymes, such as amylase and cellulase, contained in these products have been associated with IgE-mediated symptoms in occupationally exposed individuals[46–48]. Lower-level exposure to enzyme preparations has also been associated with hypersensitivity symptoms[49]. A potential concern of allergic reactions to these products should exist, although the minimum levels of exposure are not known.

## OTHER PRODUCTS

### Magnetic pillows and mattresses

Magnetic therapy has been proposed as a treatment for a variety of ailments, including snoring and OSA. The sole published report in the English language literature of magnetic therapy showed no improvement in disease severity measured by polysomnography[50]. Magnets were placed in both pillows and mattress pad in this study. There is no proposed mechanism of action and no demonstrated efficacy for either snoring or OSA.

**Table 1** Treatments for snoring or obstructive sleep apnea (OSA)

| *Proven or probable efficacy* | *Unknown efficacy* |
|---|---|
| Nasal surgery | Nasal decongestants |
| Nasal polyps | Decongestants |
| Nasal septal deviation | Anti-inflammatory nasal sprays |
| Other anatomic abnormalities | Nasal dilators |
| Pharyngeal surgery | External nasal dilators |
| Uvulopalatopharyngoplasty | Internal nasal dilators |
| Adenotonsillectomy | Nasal lubricants |
| Hyoid suspension | Dietary supplements |
| Genioglossus advancement | Magnetic therapy |
| Maxillo-mandibular advancement | Smoking cessation |
| Maxillary widening | |
| Glossopexy | |
| Radiofrequency volumetric tissue reduction | |
| Weight loss* | |
| Alcohol avoidance | |
| Position training | |
| 'Snore-ball' | |
| Oral appliances | |
| Mandibular advancement devices | |
| Tongue-retaining devices | |
| Soft palate lifters | |
| Positive airway pressure devices | |
| Nasal continuous positive airway pressure | |
| Nasal bilevel positive airway pressure | |

*Long term efficacy not established

**Table 2** Treatments for snoring and obstructive sleep apnea (OSA) with limited scientific evidence

| *Treatment* | *Proposed mechanism of action* | *Efficacy for snoring* | *Efficacy for OSA* | *Safety* |
|---|---|---|---|---|
| ENDS | enlargement of nasal cross-sectional area | inconclusive—possible role in some mild, non-apneic snorers | not demonstrated | skin irritation discomfort |
| INDS | enlargement of nasal cross-sectional area | inconclusive—possible role in some mild, non-apneic snorers | not demonstrated | discomfort displacement theoretic mucosal ulceration |
| Nasal lubricants | mucosal lubrication | inconclusive—possible role in some mild, non-apneic snorers | not demonstrated | irritation theoretic lipoid pneumonia |
| Oral dietary supplements | unknown | not demonstrated | not demonstrated | potential allergic reactions possible product contamination |
| Magnetic therapy | unknown | non | none | none |

ENDS, external nasal dilators; INDS, internal nasal dilators; ?, theoretic adverse reactions

## CONCLUSION

Treatments for snoring or OSA are summarized in Table 1. Studies of the non-prescription treatments mentioned here are of limited scientific ranking (Table 2). The efficacy of these treatments, save magnetic therapy, in snoring and OSA cannot be firmly established at this time. There is preliminary evidence to suggest the efficacy of external nasal dilator strips, internal nasal dilator and lubricant nasal and oral sprays for mild, non-apneic snoring. Studies to date have found no significant improvement in OSA. A common characteristic in the clinical series presented is a discrepancy between subjective and objective improvement in snoring and sleep quality. This is an extremely important point when counseling patients about these products, so as to avoid a potentially serious delay in the diagnosis of OSA.

## ACKNOWLEDGEMENTS

Carol Rosen MD, David Kristo MD, Jed Black MD, Michael Kohrman MD, Nalaka Gooneratne MD, Robert Neal Aguillard MD, Robert Fayle MD, Robert Troell MD and Ronald Kramer MD are thanked for their contributions.

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# 24
# The use of complementary and alternative medicine by families of children with disabilities

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*Complementary Therapies in Neurology: An Evidence-Based Approach*
Edited by Barry S.Oken
ISBN 1-84214-200-3 

The use of complementary and alternative medicine (CAM) is common by families of children with chronic conditions and disabilities. For example, studies have reported that 64% of families with children with attention-deficit/ hyperactivity disorder (ADHD)[1], 56% of families of children with cerebral palsy[2] and 50% of families of children with autism (unpublished data) have used CAM. Certain factors such as the lack of a diagnosis for the cause of the disability, the severity of the functional disability, the presence of problem behaviors, a slow rate of developmental progress and the failure of traditional treatments contribute to the decision to use CAM. In this chapter, a model is briefly presented for communication between health-care providers and families about CAM. Selected treatments are discussed for children with cerebral palsy, autism and ADHD.

What constitutes a complementary or alternative treatment? The National Center for Complementary and Alternative Medicine (NCCAM), National Institutes of Health (NIH) uses the following definition: 'CAM covers a broad range of healing philosophies, approaches, and therapies that mainstream Western (conventional) medicine does not commonly use, accept, study, understand, or make available'[3]. A complementary treatment is used in addition to conventional treatment and an alternative treatment is used in place of conventional treatment. CAM includes dietary and nutritional supplements, herbs, homeopathy, acupuncture, therapeutic touch and massage. Alternative uses are also discussed of biomedical treatments such as hyperbaric oxygen in children with cerebral palsy, and experimental treatments such as therapeutic electrical stimulation in children with cerebral palsy. New or experimental treatments have been used widely, based on the claims of proponents and a few positive case reports.

A critical issue is whether a therapy is proven or unproven and the evidence for its efficacy. A recent review of the quality of studies of complementary and alternative treatments concluded that the overall quality was poor, but improved over time, and was similar to studies of conventional treatments[4]. Most of the studies initially reviewed were rejected because they were not randomized clinical trials (RCTs), the gold standard for evidence of efficacy. Unfortunately, little research has been conducted on the use of CAM in children. The Cochrane Library's database of systematic evidence-based reviews currently contains no review of CAM and cerebral palsy, autism or ADHD, save for a review of the use of vitamin $B_6$/magnesium in autism. Large RCTs may be difficult to

conduct or inappropriate for certain issues in children with disabilities. Welldesigned single-subject research studies can provide evidence of efficacy[5,6] and will be cited as appropriate. None of the CAM treatments discussed in this chapter, however, have sufficient evidence of efficacy to recommend their use.

A recent review of research studies on risk communication and health-care decision making concluded that satisfaction with the process and certainty with the option chosen were the most sensitive and specific measures of the effectiveness of risk communication[7]. These outcomes prioritize patient and family values rather than the provider's perception of the importance of the treatment. In addition, providing more information does not necessarily assist consumers in making health-care decisions. Some individuals may be confused by large amounts of information, others may be easily swayed by how the information is presented, and some disagreements will persist even in the presence of 'evidence'[8]. One solution is to provide clear, concise information in a few key performance areas.

This chapter recommends an integrative approach to CAM and conventional treatments: consider all treatments (CAM, experimental and conventional) and support those that have evidence of efficacy and safety[9]. Provide information to families on the efficacy, safety and cost of specific treatments. In addition, provide families with information on CAM resources and make recommendations on how to interpret research studies and information from the Internet. The goals of communication about CAM are as follows: families are informed, both families and providers are satisfied with the process and families are certain about their choice[9]. The articles by Nickel and Gerlach[9], Nickel[10], and Rosenbaum and Stewart[11] present additional information and materials to assist both parents and providers in discussion of complementary and alternative treatments.

## CEREBRAL PALSY

'Cerebral palsy' is a term that refers to a group of disorders characterized by deficits in movement and posture that begin early in development. The motor deficits are non-progressive, although the manifestations may change with maturation. These disorders vary in etiology, neurological type and severity. The etiology includes chromosomal and genetic syndromes, developmental brain anomalies, congenital infections, meningitis, perinatal brain injury, periventricular leukomalacia and intraventricular hemorrhage associated with prematurity as well as other causes of brain injury. Neurological types include pyramidal (spasticity), extrapyramidal (dystonia, athetosis and ataxia) and mixed patterns of neurological involvement.

Limited information is available on the prevalence of the use of CAM by families of children with cerebral palsy. In a recent study, 56% of 213 families of children with cerebral palsy followed at a pediatric rehabilitation clinic reported the use of one or more CAM

**Table 1** Complementary and alternative treatments used by families with cerebral palsy

| |
|---|
| Dietary treatments and nutritional supplements |
| megavitamins/minerals |
| zinc |
| Herbal remedies and homeopathy |
| Chinese herbal treatment (Huatuo reconstruction pill) |
| Biomechanical therapies |
| patterning (Doman-Delacato) craniosacral therapy |
| Adeli suit |
| conductive education |
| Feldenkreis |
| hippotherapy |
| massage |
| acupuncture, acupressure |
| Alternative use of biomedical treatments |
| hyperbaric oxygen |
| Experimental treatments |
| therapeutic electrical stimulation |

treatments[2]. The most common treatments were massage therapy (25%) and aquatherapy (25%). CAM use and satisfaction with treatment outcomes in this study was strongly associated with parental use of CAM. Table 1 lists a number of the CAM treatments that are currently in use by families of children with cerebral palsy. Craniosacral therapy, the Adeli suit, conductive education, acupuncture and acupressure, hyperbaric oxygen treatment (HBOT) and therapeutic electrical stimulation (TES) will be discussed in detail.

## Craniosacral therapy

Dr John Upledger, an osteopath, developed craniosacral therapy. It is described as a gentle, hands-on approach to evaluating and enhancing the body's craniosacral system[12]. The production of cerebrospinal fluid generates a rhythm in the semi-closed hydraulic craniosacral system, and disturbances in the rhythm can be detected and corrected by craniosacral therapists. This therapy has been recommended for a variety of conditions including cerebral palsy, migraine, temporomandibular joint dysfunction, chronic fatigue, gastroesophageal reflux, birth trauma and autism[13]. Upledger claims that, if therapy is provided to young infants, many later developmental problems can be prevented.

### *Efficacy*

Several studies have failed to validate the assessment procedure, the detection of the craniosacral rhythm[14–16]. In addition, a recent systematic review of research studies on craniosacral therapy concluded that current studies provided insufficient evidence of benefit, and that research protocols were poorly designed[17]. No studies have been published specific to children with cerebral palsy. The claims that craniosacral therapy helps a variety of conditions and will prevent problems if started early should be viewed as 'red flags' by families and cause them to be very cautious in evaluating this therapy.

### *Safety*

In general, craniosacral therapy has been well tolerated. There have been few reports of complications. It is imperative, however, that craniosacral therapy be used in addition to, not in place of, conventional treatment for certain conditions. For example, craniosacral therapy has been recommended for children with hydrocephalus. Initial placement or revision of an existing cerebrospinal fluid shunt should not be delayed by craniosacral therapy.

### *Cost*

The cost of this therapy is similar to the cost of a weekly medically based physical therapy program. This includes time lost from work for a parent to attend therapy and potential interference with conventional treatments, for example, decrease in frequency of other services.

### *Resources*

www.upledger.com (Upledger Institute) and www.ucpa.org (United Cerebral Palsy Association, national advocacy group, research fact sheets).

## The Adeli suit

The Adeli suit was originally developed by the Russian space program. It is a system of elastic cords attached to rings on the jacket and trousers to increase or decrease tension across joints. The proposed mechanism of action is intensification and 'normalization' of proprioceptive impulses from joints, muscles and ligaments[18,19]. The suit has been recommended for the treatment of children with cerebral palsy and adults with head injury. A typical treatment program is 6 h of physical therapy per day (often involving three therapists), 6 days per week for 4 weeks. The child is in the suit for 1–2½ h per day. This treatment is currently available only at the Euromed Center in Poland.

### *Efficacy*

No RCTs or research studies with rigorous single subject design have been published. Euromed has presented the results of a large case series on its web site[18] and there are numerous positive anecdotal reports[18]. Euromed reports that 67% of children improve,

and that the treatment is most helpful for children 4–10 years of age with good motivation. The dependent variables and other aspects of the study's design are not presented in detail on their web site. This intervention involves intensive daily physical therapy, much of which is similar in content to conventional therapy services for children with cerebral palsy. Future studies that include a control group that receives a similar level of therapy services without the use of the suit are needed.

*Safety*

The therapy is generally well tolerated. There have been no reported complications and the risk for complications would be similar to that of conventional therapy programs with a similar intensity.

*Cost*

Treatment with the Adeli suit involves very high direct and indirect costs. The family must take time from work, travel to Poland and pay for the 4 weeks of therapy. The center provides dormitory-type accommodations for families while they are at Euromed.

*Resources*

www.euromed.pl(provider of the Adeli Suit) and www.ucpa.org (national advocacy group, research fact sheets).

**Conductive education**

Conductive education is a therapeutic approach developed at the Peto Institute in Hungary and is now available worldwide. Con-ductive education is a structured program of exercise and education that uses specially designed materials and is led by a 'conductor'[20,21]. The focus is on improving day-to-day functional skills and encouraging active learning. Skills are broken down into small steps and children are 'taught' in small groups with a social focus. Treatment involves 5 h per day 5 days per week and is ongoing. This treatment program is recommended for children with neuromuscular disorders. Conductive education is available at many sites in the USA and internationally.

*Efficacy*

A limited number of research studies have been published. Two small contemporary cohort studies reported a trend towards benefit in the conductive education group compared to a group of children who received conventional early intervention services[22,23]. In one study[23], the conductive education group showed improved motor performance and parental coping compared to children in traditional services. Both groups showed improvement on cognitive measures. A recent RCT of 34 children completed by the same investigators, however, reported no differences between children who received conductive education and children who received early intervention after 1

year of intervention[24]. Children who received conductive education and children who received early intervention made similar progress in all dimensions.

### *Safety*

No complications have been reported. The risk for complications would be similar to the risk for a child participating in a preschool or earlyschool-age program of similar intensity.

### *Cost*

The cost would be comparable to the cost of a private school program for children of a similar age.

### *Resources*

www.petoinstitute.org (Peto Institute), and www.conductive-education.org.uk (resources on conductive education) and www.ucpa.org (national advocacy group, research fact sheets).

## Acupuncture and acupressure

Acupuncture is a traditional form of Chinese medicine that involves puncturing the skin with fine needles at specific points. Acupuncture points are believed to be connected to internal organs by surface meridians or channels and internal pathways. The acupuncturist decides on which points to use to restore the circulation of the body's vital energy or *Chi* to reduce symptoms of disease[25]. Acupuncture has been used in conjunction with acupressure and massage to treat children with cerebral palsy. A treatment program may vary from ten to over 100 sessions given in 1 year. Acupuncture is available throughout the USA and internationally.

### *Efficacy*

A few single case studies have reported improvement in muscle spasms or hypertonicity with acupuncture[26,27]. A small pilot study with six children with neurological disorders and cold feet reported variable improvement in foot temperature with acupuncture[28]. Several case series of children with cerebral palsy treated by acupuncture and acupressure have been published in the Chinese medical literature[29–31]. All have reported significant overall benefit; in fact, in one study[29] 51 of 60 (85%) children were rated as improved and 12 as 'fundamentally cured'. Insufficient information was presented in the abstracts of these studies on research methodology, particularly outcome measures. The NCCAM is currently funding a study on acupuncture, hypnosis and osteopathic manipulation on muscle tension in children with spastic cerebral palsy[32].

*Safety*

Placement of the acupuncture needles results in significant discomfort for some children, and syncope is a rare complication of needle placement.[33]

*Cost*

Individual acupuncture sessions vary from approximately $50 to $100. Indirect costs include any necessary travel and parent's loss of work related to treatment sessions.

*Resources*

www.acupuncture.org (information on acupuncture) and www.medicalacupuncture.org (professional organization).

**Hyperbaric oxygen treatment**

HBOT has established efficacy for the treatment of carbon monoxide poisoning and decompression sickness (divers), and as an adjunct to the treatment of burns, wound infections, osteomyelitis and radiation tissue injury[34,35]. It has recently been applied to the treatment of individuals with acute and chronic neurological disorders including children with cerebral palsy. The proposed mechanism of action is improving tissue oxygenation and 'reactivating' areas of the brain next to the area of injury. A typical treatment for a child with cerebral palsy would involve 40 1 -hour treatments at 1.75 atm and 95–100% oxygen given twice a day, 5 days a week for 4 weeks. This treatment program is available throughout the USA and inter nationally.

*Efficacy*

Positive results have been reported in one case series (25 children)[36] and a randomized delayed entry trial of 27 children with cerebral palsy[37]. In addition, there have been a number of anecdotal reports. A recent RCT of 70 children with cerebral palsy reported no benefit for HBOT compared to a control group of children who received room air at 1.3 atm[38,39]. Both groups showed modest improvement on the primary motor outcome measure, the Gross Motor Functional Measure (GMFM). In addition, an evidenced-based review of HBOT and traumatic brain injury, stroke, multiple sclerosis and cerebral palsy sponsored by the Agency for Health Care Research and Quality, US Department of Health and Human Services, is currently being conducted by staff of the Oregon Health and Science University[40].

*Safety*

Ear pain and sinus 'squeeze' are common and some centers require children to have ventilation tubes (PE tubes) placed before treatment. Serious complications are possible,

including tension pneumothorax and seizures, although no complications were reported in the RCT of children with cerebral palsy.

*Cost*

The cost of an individual 60–90-min session varies from about $75–300, and indirect costs are also high, since one parent must accompany the child to each session.

*Resources*

www.hbot.comandwww.hbot4cpkidsfoundation.on.ca (providers of HBOT), and www.ucpa.org (national advocacy group, research fact sheets).

**Therapeutic electrical stimulation**

TES was developed by Dr Karen Pape in Toronto[41]. The treatment was developed to decrease disused muscle atrophy and spasticity and increase muscle growth and strength in individuals with chronic neuromuscular disorders. The treatment involves applying transcutaneous electrical stimulation to the muscle at a stimulus intensity just above the sensory threshold but below the threshold for muscle contraction. A typical treatment program for a child with cerebral palsy would involve application of TES nightly for 6 nights a week for as long as 2 years. The proposed mechanism of action is increase in blood flow to the muscle and thus increase in nutrients and growth factors. This treatment is available throughout the USA and internationally.

*Efficacy*

Pape and co-workers have reported a case series that demonstrated that TES improved skills and strength and decreased spasticity in children with cerebral palsy[42]. A small RCT of children who received selective dorsal rhizotomy also reported modest improvement in children who received TES[43]. Children who received TES showed limited gains in skills on the GMFM but no change in strength or spasticity compared to controls. Two RCTs have recently been published on the use of TES for 1 year in children with cerebral palsy (57 children in one study and 12 in the other)[44,45]. No benefit was demonstrated in either study on any of the outcome measures.

*Safety*

Some children experience skin irritation and muscle aches. However, no significant sideeffects have been reported in the RCTs.

*Cost*

The cost of this treatment includes the cost of the equipment, approximately $1000, and the cost of regular follow-up evaluations with the therapist. Pape emphasizes the importance of using TES along with conventional treatments.

*Resources*

www.mayatek.com (supplier of stimulator), www.cerebralpalsyny.org (provider of TES) and www.ucpa.org (national advocacy group, research fact sheets).

## AUTISM

Autism is a behavioral syndrome characterized by deficits in communication, social skills and play. The etiology varies and includes chromosomal (e.g. Down syndrome) and genetic syndromes (e.g. tuberous sclerosis and fragile X), congenital cytomegalovirus infection and perinatal brain injury. The majority of children with autism, however, do not have an

**Table 2** Complementary and alternative treatments used by families of children with autism

| |
|---|
| Dietary treatments and nutritional supplements |
| vitamin $B_6$/magnesium |
| vitamins C and A |
| megavitamins |
| gluten- and casein-free diet |
| Feingold diet Herbal remedies and homeopathy |
| Biomechanical therapies |
| craniosacral therapy |
| hold therapy (squeeze machine) |
| brushing, massage |
| music therapy |
| rhythmic entrainment |
| Alternative uses of biomedical treatments |
| anti-yeast therapy (nystatin) secretin |
| intravenous immunoglobulin, transfer factor |
| famotidine (Pepcid®) |
| chelation |
| Experimental treatments |
| auditory integration training |
| facilitated communication |

identifiable cause for their disability[46]. Thirty per cent of children with autism appear to develop typically for the first 18–20 months and then regress in language, behavior and social skills. In addition, a number of studies have reported an increase in the prevalence of autism[47–50].

The cause or causes of the developmental regression and the apparent increase in the prevalence of autism have not been established. A number of theories have been proposed to explain these changes; for example, yeast overgrowth due to frequent antibiotic use, absorption of biologically active peptides from gluten and casein in the toddler's diet, reaction to the mumps, measles and rubella (MMR) vaccine and reaction to thimerosal (mercury) used as a preservative in vaccines. CAM treatments and related laboratory tests have been developed for each of these theories. The Institute of Medicine has recently released evidenced-based reports on the MMR vaccine and autism and thimerosal and autism[51,52]. Insufficient evidence was found to support the claims of an association between the MMR vaccine and autism or thimerosal received from routine vaccinations and autism.

In 1995, 50% of the parents who responded to a survey of families of children who were receiving services through the Regional Program for Autism, Oregon Department of Education, reported use of one or more CAM treatments with their child (unpublished data). In 2001, 64% of parents who responded to a similar survey of families of children participating in the Lane Regional Program, Lane County, Oregon, reported use of one or more CAM treatments with their child (unpublished data). The most frequent CAM treatments were vitamin $B_6$/magnesium and dimethyl glycine in both surveys. In the 2001 survey, 35.6% of parents reported use of two or more CAM treatments. Table 2 lists many of the CAM treatments used by families of children with autism. The use of vitamin $B_6$/magnesium therapy, dimethyl glycine, a gluten- and casein-free diet, anti-yeast therapy, secretin, intravenous immunoglobulin (IVIG) and auditory integration training (AIT) will be discussed in detail. A recent review of CAM and autism is available[53].

## Vitamin $B_6$/magnesium

Vitamin $B_6$ (pyridoxine) is an essential co-fac-tor in amino acid metabolism and is involved in the formation of serotonin, a neurotransmitter[54]. It has been used to treat individuals with a number of different neurological disorders including seizures, headaches, peripheral neuropathies, movement disorders and depression. It is given with magnesium in children with autism to potentiate the effect of the pyridoxine. A typical dose of vitamin $B_6$ for children with autism is 8 mg per pound (0.45 kg) of weight and about one-third of that dose of magnesium[55].

### *Efficacy*

The Cochrane Review found insufficient evidence to make a recommendation, owing to the limited number (only two RCTs) and inadequate quality of the studies and the small sample sizes[56]. Two previous systematic reviews of trials of $B_6$ and other vitamins reached similar conclusions[57,58]. In one of these reviews[57], five of the studies involved vitamin $B_6$ with or without magnesium and children with autism. All five studies had

serious methodological shortcomings and all had small sample sizes. Of interest, a review of studies on vitamin $B_6$/magnesium written by Rimland (a proponent of vitamin $B_6$/magnesium therapy) which is available through the Autism Research Institute concludes '…published studies prove beyond a doubt that a substantial portion of autistic children and adults show worthwhile benefits…'[59].

### *Safety*

No side-effects were reported in the two RCTs[60,61]. Peripheral neuropathy has been reported in adults with chronic use of high doses of $B_6$ (2–6 g/day)[62]. Children treated with moderate doses over a long period of time may be at risk for a similar problem. The sideeffects noted by some parents in the Oregon survey included gastrointestinal upset and difficulty getting their child to take the preparation.

### *Cost*

Rimland has estimated the cost to vary from about $4 to $20 per month and provides information on obtaining vitamin $B_6$/magnesium (Super Nu-Thera formula) on the Autism Research Institute's website.

### *Resources*

www.autism.com/ari (Autism Research Institute, resources on alternative therapies) and www.autism-society.org (Autism Society of America, national advocacy group with local chapters).

## Gluten- and casein-free diet

The proponents of this CAM treatment claim that children with autism have a 'leaky gut' which results in the absorption of peptides that act as endogenous opioids and contribute to the behavioral symptoms of autism[53]. A number of theories have been proposed to explain the 'leaky gut' and the developmental regression at 18–20 months in some children with autism. These include exposure to cow's milk and wheat, yeast overgrowth from antibiotic use, reaction to the MMR immunization and a primary immunological problem. The association of the MMR vaccine, enterocolitis and autism remains controversial[63]. Recent studies have made clear that a number of children with autism have undiagnosed gastrointestinal (GI) problems, particularly gastroesophageal reflux, which may contribute to their behavioral problems[64,65].

### *Efficacy*

One small single-blind RCT has been published[66]. The study had a number of methodological limitations but did report improved development at 1 year for the children on the diet compared to controls. A number of anecdotal reports also claim benefit for the diet. Two small double-blind challenge studies with gluten in children with autism, however, reported no change in behavior or GI symptoms with the challenge[67,68].

*Safety*

The diet is difficult to follow and concern has been expressed about potential nutritional deficiencies. One study compared the nutrient intake of eight children with autism on the diet with 29 children eating a regular diet[69]. Both groups showed nutritional deficiencies. A general recommendation is that parents who plan to use the diet contact a nutritionist and also provide calcium and vitamin D supplements to their child.

*Cost*

The cost includes the direct cost of laboratory testing (for example, $200–300 for food allergy testing and gluten/casein peptide test), and the indirect cost of the time for meal preparation.

*Resources*

www.glutensolutions.com and www.glutenfree.com (resources on the diet), www.autism.com/ari (Autism Research Institute) and www.autism-society.org (national advocacy group).

**Anti-yeast therapy**

As commented, one theory for the regression seen in some children with autism is yeast overgrowth from frequent use of antibiotics or a primary immunological problem, development of a 'leaky gut' and absorption of biologically active substances. The CAM treatment involves use of oral nystatin to decrease the amount of yeast antigens and a probiotic diet. Proponents recommend obtaining urinary organic acids and stool cultures for yeast before and during treatment. Limited age-specific normative data, however, are available to guide interpretation of high or low values of these tests. Some studies have confirmed an increase in urinary organic acids in individuals with autism[70] and others have not[71,72].

*Efficacy*

A great deal of anecdotal information is available on the Internet and elsewhere that supports the benefit of this treatment. No RCTs, studies with single-subject design or case series have been published.

*Safety*

Some children experience diarrhea and other GI side-effects. In general, oral nystatin is well tolerated and has been used frequently in pediatrics to treat oral candidiasis.

### *Cost*

The cost includes the cost of laboratory testing (at least $200–300 for initial organic acid testing and yeast culture with sensitivity), and the cost of the nystatin prescription and the probiotic products (nutritional supplements).

### *Resources*

www.autism.com/ari (Autism Research Institute), www.kirkmanlabs.com (resource for probiotics) and www.autism-society.org (national advocacy group).

## Secretin

Secretin is a pancreatic hormone important in digestive function. A recent report of behavioral improvement in three children with autism following use of secretin as an adjunct to the evaluation of GI problems[71] has resulted in a worldwide interest in secretin as a treatment for autism as well as a focus on a possible brain-gut connection in autism. Secretin receptors are present in the brain with secretin immunoreactivity highest in the cerebellum[73]. Porcine and synthetic secretin have been given by infusion and transdermally, as a single injection and as a sequence of injections to hundreds of children with autism since the initial case report.

### *Efficacy*

Eight RCTs of a single intravenous infusion of secretin (sample sizes varied from eight to 95) have been published to date and none have reported benefit in children with autism[74–81]. In addition, one small RCT of three sequential doses of secretin reported no benefit[82]. A small RCT of secretin and children with autism and GI problems, however, reported benefit in the subgroup of children with chronic, active diarrhea only[83].

### *Safety*

In general, the intravenous infusion of secretin has been well tolerated in the RCTs. The Autism Research Institute has collected responses from families and physicians worldwide[84]. Some children have shown an increase in hyperactivity or aggressive behavior that resolved in 1–2 weeks, and a few children have had seizures. One child had an apneic episode at the time of the infusion. These rare compli-cations underline the importance of providing secretin infusions in an appropriately equipped medical setting.

### *Cost*

The cost of this treatment includes the office visit for the infusion, the cost of secretin (approximately $300 per vial) and the possible indirect costs of parental time lost from work.

*Resources*

www.autism.com/ari (Autism Research Institute), www.autism.com/ari/editorials/safety (safety information on secretin), and www.autism-society.org (national advocacy group).

**Intravenous immunoglobulin**

A great deal of research has explored possible immunological causes of autism. Studies have reported abnormalities of T cells, B cells, natural killer (NK) cells and macrophages, and the presence of autoantibodies in children with autism[85]. Although a variety of abnormalities have been reported, no consistent immunological changes in individuals with autism have been found[86]. All of the autoantibodies detected in autism also occur in other neurological disorders and in controls. Nevertheless, a number of immunological treatments have been proposed, including use of IVIG and transfer factor. A typical treatment program with IVIG would involve infusions of 400 mg/ kg every 4 weeks for as long as 6 months.

*Efficacy*

Three open-label studies of IVIG in children with autism have been published, but no RCTs[87–89]. Gupta and co-workers[87] reported subjective improvement in ten of ten children and commented that younger children responded the best. The other two studies have failed to replicate these results. Plioplys[88] reported improvement in only one of ten children, and DelGiudice-Asch and co-workers[89] (most rigorous research design) noted no improvement in any of the five children treated.

*Safety*

No significant complications were reported in the three open-label studies. Serious complications are possible including infection, seizures and renal failure[86].

*Cost*

The cost of IVIG treatment is high; $5000 or more in direct costs and high indirect costs related to possible parental loss of work to accompany the child to each session.

*Resources*

www.autism.com/ari (Autism Research Institute) and www.autism-society.org (national advocacy group).

**Auditory integration training**

AIT is based on the work of Guy Berard, a French physician[90]. Some individuals with autism have extreme auditory sensitivity. Berard theorized that treatment with broadband sound filtered to eliminate the individual's peaks of hearing sensitivity would decrease

the auditory sensitivity and improve cognitive and behavioral functioning. A typical treatment program involves listening to electronically modulated music through earphones twice daily for 30 min for 10 days. This CAM treatment is available throughout the USA and internationally.

### *Efficacy*

Dawson and Watling reviewed five studies of AIT in autism[91]. Only three of the studies contained a control condition. Two of these studies showed similar changes in both experimental and control groups. The third study reported greater improvement in children treated with AIT. However, there were significant pretreat-ment differences between the groups. Since the review by Dawson and Watling, another controlled trial of AIT in autism has been published[92]. Children in the control group were superior on parent-rated measures of hyperactivity and no other between-group differences were noted. In addition, the American Academy of Pediatrics has published a policy statement recommending against the use of AIT based on insufficient evidence of efficacy[93].

### *Safety*

Some children have shown an increase in hyperactivity and other problem behaviors. Otherwise, no complications were reported in the studies cited above.

### *Cost*

The cost of a 10-day treatment program is approximately $1500.

### *Resources*

www.up-to-date.com/saitwebsite (Society for Auditory Integration Techniques, provider of AIT) and www.autism-society.org (national advocacy group).

## ATTENTION-DEFICIT/HYPERACTIVITY DISORDER

ADHD is a behavioral disorder characterized by inattention, distractibility, over-arousal and impulsivity. It is associated with academic underachievement and low self-esteem. ADHD is the result of the interaction of genetic, biological and environmental factors. It has a strong familial basis. Biological factors include prenatal alcohol and drug exposure, meningitis, metabolic encephalopathy, traumatic brain injury and other causes of brain injury. The conventional treatment of ADHD is multimodal: medication, behavioral and educational interventions and family support. Several reviews of CAM and children with ADHD are available[94–96].

Families of children with ADHD frequently use CAM. In one study, 64% of parents reported using one or more CAM treatments with their child[1]. In another study, 80% of 100 consecutive families of children with ADHD seen in a clinic reported the use of a special diet[97]. The Feingold diet and sugar-elimination diets are the most commonly used

CAM treatments by these families. Table 3 lists many of the CAM treatments used by families of children with ADHD. The Feingold and sugarelimination diets, dietary supplements, herbal remedies and neurofeedback are discussed in detail.

### Elimination diets

In 1975, Feingold, an allergist, proposed that artificial colors, preservatives and naturally occurring salicylates were an important cause of hyperactivity, and recommended treatment with an elimination diet[98]. He had noted that the increase in children with hyperactivity seemed to parallel an increase in the use of artificial salicylates as food additives. He claimed that as many as 50% of children would

**Table 3** Complementary and alternative treatments used by families of children with attentiondeficit/hyperactivity disorder

| |
|---|
| Dietary treatments and nutritional supplements |
| Feingold diet |
| sugar-elimination diet |
| allergy-based diet |
| megavitamins/minerals |
| vitamin B6/magnesium |
| iron |
| zinc |
| essential fatty acids |
| Herbal remedies and homeopathy |
| Biomechanical therapies |
| craniosacral therapy |
| sensory integration therapy |
| Alternative uses of biomedical treatments massage |
| anti-yeast therapy (nystatin and diet) |
| antihistamines |
| neurofeedback (electroencephalogram biofeedback) |
| vision training, colored lenses |
| nootropics (piracetam) |

improve when treated with the elimination diet. Detailed dietary information is available through the web site of the Feingold Association.

Another popular dietary treatment is the elimination of sugar (sucrose). The Feingold diet does not eliminate sugar.

### *Efficacy*

Wender reviewed existing trials of the cial colors (tartrazine) in 1986[99]. She con-Feingold diet and food challenges with artificluded that there was no evidence that the Feingold diet was efficacious in the treatment of ADHD, although she also noted that a few children did appear to respond in some studies. A small RCT published since that review reported similar overall conclusions; however, it also reported that a few children appeared to respond to a food dye challenge and an elimination diet[100].

In 1995, Wolraich and co-workers conducted a systematic review of 16 RCTs on the effect of sugar on the behavior of children with ADHD[101]. They concluded that there was no evidence that sugar adversely affected the behavior or cognitive performance of children with ADHD. No further RCTs have been published since that review.

### *Safety*

Concern has been expressed about possible vitamin C deficiency with the Feingold diet. No data have been presented related to this concern.

### *Cost*

The primary cost to the family is the time necessary to prepare and monitor the diet.

### *Resources*

www.feingold.org (Feingold Association) and www.chadd.org (Children and Adults with Attention-Deficit/Hyperactivity Disorder, national advocacy group, fact sheets).

## Nutritional supplements

A variety of studies on the use of nutritional supplements in children with ADHD have been published recently, including a few small RCTs. Particular interest has been paid to supplementation with essential fatty acids (EFA) (fish oil, docosahexaenoic acid (DHA), evening primrose oil (EPO) and zinc. Fish oil contains eicosapentaenoic acid (EPA) and DHA (both ω-3 fatty acids), and EPO contains linoleic acid (ω-6 fatty acid) and γ-linolenic acid (ω-3 fatty acid)[94]. Two previous studies have reported that children with ADHD had lower ω-3 fatty acid levels[102] and that children with low ω-3 fatty acids had significantly more behavior, sleep and learning problems[103]. Proponents of fish oil supplementation also point to a similarity in the symptoms of fatty acid deficiency and the symptoms of children with ADHD[104]. In addition, Arnold and coworkers[104] have reported an apparent association between EFA and zinc blood levels in children with ADHD and an association between response to EFA supplementation and zinc status. Zinc also has been suggested as a factor in the pathogenesis of ADHD, and studies have reported an association between low zinc hair and blood levels and ADHD[105,106].

Supplements of fish oil, DHA, EPO and zinc are readily available at health food stores. Flax seeds and sea food are also excellent sources of ω-3 fatty acids. The recommended dose of fish oil (ω-3 fatty acids, EPA and DHA) is 500–1000 mg/day and EPO 500 mg 3–6 times per day[94].

### *Efficacy*

The four RCTs of EFA supplementation of children with ADHD have reported very limited evidence to support efficacy[107–110]. In one study[110], 63 children with ADHD received either 345 mg/day of DHA or placebo for 4 months. No differences were noted between the two groups on any of the objective or subjective outcome measures. Richardson and Puri[109], however, reported significant improvement on three of 14 outcome measures in 41 children with ADHD and learning problems supplemented with EFA. Two additional studies of EPO supplementation of children with ADHD reported statistically significant improvement of the experimental group vs. controls on only one of multiple outcome measures[108] and two of 42 measures, respectively[107].

### *Safety*

The side-effects of fish oil include flatus and halitosis[94]. In addition, use of fish oil may increase bleeding time and should not be used with anti-platelet drugs or anti-coagulants, or by individuals with bleeding disorders.

### *Cost*

The monthly cost of supplementation varies from about $5 to $20.

### *Resources*

www.supplementwatch.com, (private group, information on supplements) and www.chadd.org (national advocacy group).

## Herbal remedies and homeopathy

Sedative herbs are among the most commonly used herbal remedies by families of children with ADHD. Children with ADHD have difficulty concentrating, show overactivity and frequently have sleep disorders. Herbalists have traditionally used sedative herbs to treat poor concentration, restlessness and sleep problems[94]. Sedative herbs include valerian, lemon balm, kava, chamomile and passion flower. Other herbal products touted as treatments for ADHD include ginkgo biloba, pycnogenol and blue-green algae. No RCTs or open-label studies of herbal treatments for ADHD or sleep disorders in children have been published. An excellent review of herbal treatments for children with ADHD has been published[94] and includes descriptions of the most commonly used herbal products, usual doses, sideeffects and potential drug interactions. Resources for evidence-based reviews of many herbal remedies include www.mcp.edu/herbal (the website of the Longwood Herbal Task Force) and

www.herbmed.org (a project of the Alternative Medicine Foundation, Inc.). Health professionals should become familiar with the herbal treatments commonly used for ADHD, the rationale for their use, the usual doses and their side-effects. The potency of these products may vary considerably[111].

## Neurofeedback

Electroencephalogram (EEG) biofeedback is a training program designed to 'improve mental performance, change behavior and stabilize mood'[112]. The individual is trained to reinforce specific EEG frequencies and inhibit others. Neurofeedback has been used to treat ADHD, depression, epilepsy, post-traumatic stress disorder, Tourette syndrome, sleep disorders, traumatic brain injury, migraine headaches, tinnitus, chronic fatigue, alcoholism and addiction[112]. Dr Joel Lubar and co-workers at the University of Tennessee began to use neurofeedback to treat children with ADHD in the mid-1970s[113]. A typical treatment program for attention and behavior problems involves 20–40 sessions, of 30–45 min, twice weekly, and may extend to 100 or more sessions. Children as young as 2 to 3 years of age have participated in treatment. Neurofeedback is available throughout the USA and internationally.

### *Efficacy*

Several case series as well as one clinical trial with a waiting-list control group have been reported[114–116]. Children have been reported to improve attention and behavior as well as IQ scores in some studies. Improvement appeared to be associated with decreased theta activity or decreased theta/beta ratios[114,115]. Unfortunately, no RCTs have been published. In addition, the existing studies have a number of methodological flaws, including inadequate description of subjects, limited outcome measures and failure to use independent examiners blinded to the subjects' treatment status.

### *Safety*

No significant side-effects have been reported. Some participants have developed headaches or fatigue after neurofeedback.

### *Cost*

The cost of this treatment program is potentially very high. The charge for a single session is approximately $50–125.

### *Resources*

www.eegspectrum.com (provider of neurofeedback) and www.chadd.org (national advocacy group, fact sheets).

## SUMMARY

The families of children with disabilities are likely to try CAM treatments with their child. The responsibilities of health-care providers are: to assure access to conventional treatments; consider all treatments and support those with evidence of efficacy and safety; provide information on efficacy, safety and cost of specific treatments; know local CAM resources; provide guidance on interpreting research studies and information from the Internet; assist families in keeping a symptom diary; and continue to support families whether they choose to pursue an unproven treatment[9]. The responsibilities of parents are to inform their health-care provider on all treatments they are using including CAM therapies; be informed about any therapy they are considering (do their homework!); identify key target symptoms/behaviors and keep a symptom diary; continue one treatment long enough to determine if it is effective and make only one change in treatment at a time; and, finally, recognize that providers cannot provide everything[9].

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# 25
# Psychiatric disorders

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*Complementary Therapies in Neurology: An Evidence-Based Approach*
Edited by Barry S.Oken
ISBN 1-84214-200-3 

## INTRODUCTION

The purpose of this chapter is to increase the awareness and knowledge regarding complementary and alternative medicine (CAM) and broadly defined psychiatric conditions in the hope of making this information relevant to the practice of clinical neurology. The claims, prevalent beliefs and research evidence for several commonly used treatments or practices will be summarized for the topics of anxiety, depression, schizophrenia, substance abuse and sexual dysfunction. Other topics generally included in psychiatric diagnostic categories such as dementia are covered in other portions of this book (see Chapter 18).

The mental, emotional and behavioral characteristics of patients with neurological conditions can complicate the neurological diagnostic picture and influence the patient's response to their condition as well as their response to treatment. The extensive use of CAM in the USA and in all parts of the world has been well documented, and physicians must be aware of CAM treatments and practices that also may influence the diagnostic picture as well as interfere with or potentiate standard medical treatments.

The use of CAM by patients and the reasons for this use can reveal attitudes and beliefs regarding treatment of any kind. A recent survey by Astin indicated that CAM users found CAM to be more congruent with their values, beliefs and philosophical orientations toward health and life[1]. Thus, CAM utilization may serve as a means to achieve the understanding that is important in the establishment of rapport with patients and their families.

In addition, there are a significant number of physicians who believe in the efficacy of at least some CAM treatments and refer patients to CAM practitioners, as well as practicing some CAM treatments themselves[2]. While these considerations are not 'psychiatric' in the sense that they are indicative of pathology, they are indicative of the 'psychology' of individuals and their referring physicians that may have a bearing on their attitudes and responses to their neurologic and co-morbid psychiatric conditions. This is particularly important when dealing with multicultural populations where the basic understanding and interpretation of broadly defined psychiatric conditions and characteristics may be considerably different from those of the majority population.

There are methodological issues that must be addressed briefly regarding the evidence to be presented in this chapter. Given the fact that in a summary issued by the Office of Alternative Medicine (the predecessor to the current National Center for Complementary and Alternative Medicine) there are estimated to be more than 700 journals that have content pertaining to CAM, and, given that the majority of these are not in the English language, there will be a wide variety of evidence[3]. The definition of evidence-based medicine used here is that it is a process of turning clinical problems into questions and then systematically locating, appraising and using contemporaneous research findings as the basis for clinical decisions[4]. However, when evaluating the evidence for its validity and clinical usefulness, a large proportion of published research lacks either relevance or sufficient methodological rigor to be reliable enough for answering clinical questions[5].

It is also important to define the terms ‘efficacy’ and ‘effectiveness’ as they apply to research information that can be relied upon for clinical decision-making. The Agency for Healthcare Research and Quality has defined efficacy research as the effort to clearly demonstrate relationships between treatment and outcomes under controlled or ‘ideal’ conditions. Efficacy studies attempt to use the most powerful and sophisticated research designs such as randomized clinical trials, which use homogeneous groups of patients (subjects) with similar disorders, similar levels of severity and similar demographic characteristics. The outcome measures are determined in advance, and it is important that all individuals receiving the treatment and those not receiving the treatment be measured in the same manner by the same tests. Control over extraneous factors is addressed by using random assignment to groups and by maintaining a high level of consistency and standardization in the administration of the treatment and the assessment of the outcome. Effectiveness, on the other hand, is defined by the Agency for Healthcare Research and Quality as the ability to show that an intervention produces change in a typical clinical or natural setting, i.e. in facilities with a staff of average competency, practical levels of funding and the normal range of variation in patients served[6].

The implementation difficulties regarding true experiments may be specially difficult for other cultures and researchers with limited research capacity. The difficulties include obtaining an appropriate sample size, the ability to assign participants randomly to groups or conditions, the difficulty inherent in providing the same type, level, or intensity of treatment to all persons in the treatment groups, the problem of using the same standardized measure for assessing outcome in all subjects, the feasibility of masking the treatment and outcome measures and the ethical objections associated with denying treatment to participants in control or placebo conditions[7,8].

A final methodological observation is that there may be essential differences in outcome intentions between CAM and standard medical practices. The unit of analysis in some CAM treatments may be a holistic, health-oriented approach to the patient rather than a diseaseoriented diagnostic and treatment model. Holistic health care emphasizes the inclusion of the individual’s mind, body, emotions, spirit and environment in the development of selfhealing and self-care, and is inclusive of a wide range of health-care practices. Thus, the diagnostic terms and the measured outcomes may be difficult to combine with existing standardized nomenclature and measures. In mental health, diagnosis and treatment outcome are typically based on verbal and other behavior, often using interview and self-report and the reports of others. Self-perception, tolerance of aberrant behavior, religious beliefs and social role performance can be essential

components of the definition of mental illness or impairment and these have strong cultural and socioeconomic determinants.

Given these methodological issues, it is only in rare instances that there is research with consistent characteristics sufficient to permit meta-analyses that can lead to summary concepts such as effect size and risk ratios which, in turn, can lead to clinical decision-making based on available relevant research evidence. Even given this optimal situation, the decisionmaking may not be easy to determine—as will be described in the use of *Hypericum* or St John's wort for the treatment of depression. In contrast, much of the research available on CAM consists of early reports, case studies, animal analog studies and studies illustrating treatment practices that are performed by advocates. The results are often worthy of being followed by more formal research, and replications that increase the risk of disconfirmation. However, the task is a large one. In a recent summary of the most commonly used herbal and aroma therapies, 65 preparations are listed as having potential effects on conditions such as anxiety, sedation, depression, manic conditions, mood elevation, panic attacks, sleep disorders, agitation, anger and muscle relaxation. In addition, one needs only to look at the National Institutes of Health (NIH) web site dealing with the International Bibliographic Information on Dietary Supplements (IBIDS) to realize the vast scope of existing research even in this restricted area. Ginkgo alone has 421 peer-reviewed references[9].

## CONDITION-SPECIFIC TREATMENTS

In this chapter, certain treatments, particularly herbal preparations, are generally intended to treat particular conditions, such as anxiety or depression. These treatments or preparations will be described in this section of the chapter. However, there are many treatments or healthcare practices, such as acupuncture, that are used to treat many different conditions or health problems. These larger systems are described in the later section of the chapter entitled *Treatments and systems addressing multiple conditions.*

In introducing herbal preparations it is important to note that the quality control standards applied by the Food and Drug Administration (FDA) are those applied to foods rather than pharmaceutical or over-the-counter (OTC) drug quality standards. There is little reliability in content and quality control for most herbal preparations sold in health food stores, pharmacies and supermarkets, and poor manufacturing practices and false advertising still exist. Germany and Britain have developed useful quality standards that can generally be depended on in products imported from European countries or claiming to meet those standards in US products (such claims, if false, are actionable by the Federal Trade Commission).

### Depression

#### *St John's wort*

A systematic review by Ernst and co-workers concluded that depression is one of the most common reasons for using CAM and that rigorous scientific data are extremely limited[10]. The areas that they believed had the most evidence for beneficial effects are

exercise, herbal therapy with St John's wort *(Hypericum perforatum)* and, to a lesser extent, acupuncture and relaxation therapies. A variety of research methods have been used to investigate this preparation, i.e. placebo controls, comparison with established antidepressants, large-scale post-market reporting and animal research.

One meta-analysis by Linde and Mulrow for the Cochrane Depression, Anxiety and Neurosis Group summarized the results of 27 trials including the criteria of 2291 patients[11]. A total of 17 trials with 1168 patients were placebocontrolled (16 addressed single preparations, one a combination with four other plant extracts). Ten trials (eight single preparations, two combinations of hypericum and valerian) with 1123 patients compared hypericum with other antidepressant or sedative drugs. Most trials were 4–6 weeks long. Participants usually had 'neurotic depression' or 'mild to moderate severe depressive disorders.' The review concluded that

> 'Hypericum preparations were significantly superior to placebo (rate ratio 2.47; 95% confidence interval 1.69 to 3.61) and similarly effective as standard antidepressants (single preparations 1.01; 0.87 to 1.16, combinations 1.52; 0.78 to 2.94). The proportions of patients reporting side-effects were 26.3% for hypericum single preparations vs. 44.7% for standard antidepressants (0.57; 0.47 to 0.69), and 14.6% for combinations vs. 26.5% with amitriptyline or desipramine (0.49; 0.23 to 1.04). There is evidence that extracts of hypericum are more effective than placebo for the short-term treatment of mild to moderately severe depressive disorders. The current evidence is inadequate to establish whether hypericum is as effective as other antidepressants. Further studies comparing hypericum with standard antidepressants in well defined groups of patients over longer observations periods, investigating long term side-effects, and comparing different extracts and doses are needed.'

A recent five million dollar multi-site trial compared the efficacy and safety of a well-characterized *H. perforatum* extract (LI-160) with an active comparator (sertraline) in major depressive disorder[12]. A double-blind, randomized, placebo-controlled trial was conducted in 12 academic and community psychiatric research clinics in the USA. The subjects were 340 adult out-patients with major depression and a baseline total score on the Hamilton Depression Scale (HAM-D) of at least 20. Dosages of both treatments were adjusted according to clinical response. Responders at week 8 could continue blinded treatment for another 18 weeks. The outcome measures were the HAM-D and the Clinical Global Impressions Severity measure (CGI-S). Of the 340 acute-phase subjects, 245 (72%) completed 8 weeks, 129 (38%) entered the continuation phase, and 79 (23%) completed continuation. On the two primary outcome measures, neither sertraline nor *H. perforatum* was significantly different to placebo. Sertraline was better than placebo on the CGI Improvement measure (CGI-I) ($p$=0.02), which was a secondary measure in this study. The authors concluded that the study failed to support the efficacy of *H. perforatum* for moderately severe major depression.

There has been considerable discussion regarding this study that pertains to all research on herbal preparations. For instance, the authors pointed out the importance of including active and inactive comparators. Without a placebo, hypericum could have

been considered as effective as sertraline (a finding in several studies with standard antidepressants). Without sertraline as an active comparator, the results would have been interpreted as evidence for the lack of efficacy of hypericum.

The authors added further qualifications regarding the standardization basis for the preparation used in this study. 'Although the hyperforin content of this batch was 3.1%, the formulation was not standardized to hyperforin, which has been suggested by some as an important active ingredient.'[13,14]

There have been several criticisms of the study. For instance, dosage levels of the treatments may have been too low to elicit treatment effects. In addition, the effect of herbal preparations may have been due to multiple active ingredients at low concentrations. Individual ingredients may not work well when separated for standardization[15].

The differences between studies conducted in the USA and the UK with those conducted in Germany (described above) could be due to the fact that the US sample may have included unresponsive patients. The German trials studied patients with mild to moderately severe depression treated by general practitioners or psychiatrists in private practice. In contrast, about 65% of the participants in the two US studies had prolonged depressive symptoms for more than 6 months[16].

Another common problem in placebo-controlled research concerns the characteristics of the placebo. Sertraline has more physiological effects than placebo or hypericum, and subjects were not completely blinded to treatment assignment, potentially leading to falsely elevated treatment effects. Lack of attention to rater blinding may have led to over-interpretation of results on the secondary clinical rating measure. The relationship between CGI-I outcome and clinician guesses of treatment assignment was not reported. Other reviews have discussed the necessity of using active placebos, i.e. having side-effects similar to those of the antidepressant under test[17] . This issue is covered in detail by a recent Cochrane review[18].

A major issue pertains to all the studies of depression treatments reported in this chapter. Established antidepressants have failed to show superiority in up to 35% of trials[19]. Another review reinforces the concept of minimal differences between active and placebo responses as indicated by suicide rates[20]. The authors of the multi-site study state that their finding 'illustrates the difficulties plaguing randomized placebo-controlled trials in this population'. They continue, 'An increasing number of studies have failed to show a difference between active antidepressants and placebo. Many of the presumed factors underlying this phenomenon were carefully attended to in this study, e.g., adherence to quality control by rater training, treatment adherence monitoring, inclusion of experienced investigators, and carefully defined entry criteria. Despite all of this, sertraline failed to separate from placebo on the 2 primary outcome measures.'

Returning to the issue of evidence-based medicine, this research and its commentaries provide a good summary of the complex issues that are involved in conducting and interpreting research of this kind. Skeptics have used this research as 'proof' that St John's wort is ineffective. Advocates have stated that the research was not an adequate test of either sertraline or St John's wort. One review provides a critique of multicenter research[21]. Some might conclude that sertraline was also found to be ineffective, although it is generally accepted as a known and effective antidepressant. Conventional and complementary health practitioners and consumers will probably not change their minds

as a result of this research. For instance, the authors concluded that 'hypericum should not be used for milder depression until trials show clear evidence of efficacy and should not be substituted for standard clinical care of proven efficacy, including antidepressant medications and specific psychotherapies, for the treatment of major depression of moderate severity.'

Of immediate concern are potential negative side-effects and adverse drug reactions resulting from the use of herbal preparations. One recent review dealt with the fact that older people with dementia are often prescribed numerous medications and often use herbal therapies in addition to these conventional drug therapies[22]. The authors identified a series of potential interactions between herbal and conventional drug therapy that place older people at risk for adverse drug events.

Useful reviews of herbs, botanicals and other products can be found at the Memorial Sloan-Kettering Cancer Center web site[23]. Regarding St John's wort, the site provides the following cautionary summary:

> 'St John's wort can interact with many medications due to induction of cytochrome p450 3A4 and other mechanisms. Significant interactions include decreased efficacy of anti-retrovirals, cyclosporin, tacrolimus, antiepileptics, irinotecan and other chemotherapeutic agents. Serotonin syndrome may occur when combined with sympathomimetics, antidepressants, or triptans (serotonin 5HT-1 agonists). Common adverse reactions included headache, nausea, abdominal discomfort, constipation, dizziness, confusion, fatigue, dry mouth, sleep disturbances, and sedation. Infrequent reactions included photosensitivity or photodermatitis, elevated liver function tests, acute neuropathy, increased PT.'

The review concluded that: 'St John's wort should not be taken with other medications and should be used under medical supervision.' Special warnings concerned potential photosensitivity, the recommendation for discontinuation 1 week before surgery or chemotherapy, and the contraindication for pregnant or nursing women.

### *L-tryptophan and 5-hydroxytryptophan*

5-Hydroxytryptophan (5-HTP) is synthesized from the amino acid tryptophan. It then produces serotonin, which has an established relationship to the symptoms of depression. Tryptophan herbal preparations were widely used without notable harm until the 1989 epidemic outbreak of eosinophilia-myalgia syndrome (EMS) in the USA. More than 1500 cases of EMS, including at least 37 deaths, were reported by the national Centers for Disease Control and Prevention (CDC). In 1990, the FDA banned the public sale of dietary L-tryptophan.

While more than 95% of the cases of EMS were traced to L-tryptophan supplied by Showa Denko K.K. of Japan, which used a novel but now discontinued process of genetic engineering to increase the production of tryptophan, the cause-and-effect relationship between tryptophan and the disease proved to be more complex. There are several articles and summaries dealing with this issue. While the ban continues on the herbal form of L-tryptophan, pharmaceutical preparations have been approved and are available in the

marketplace, including the computer web sites. L-Tryptophan is used in certain food formulations, in animal feed and in veterinary medicine. On one web site it appears that it is available for, 'Dr.'s, Chiropractors, Hospitals, Clinics as well as non-medical professionals.'[24] Basically, it appears that L-tryptophan is available for the treatment of depression and several other maladies (see web site), and the issue of EMS has remained unresolved.

A comprehensive summary of the background, controversy and complex US Federal rulings is available from the US FDA report[25]. Another summary of a strongly held viewpoint is signaled by the title of the report appearing on the Web (Smart Drug Update: The FDA Ban of L-Tryptophan: Politics, Profits and Prozac)[26].

The most comprehensive overall summary has been supplied by the Cochrane Review, selections of which are quoted below[27]. Regarding the relationship to EMS, the authors state:

> 'The nature of the tryptophan-EMS association has not yet been fully elucidated. It is also possible it is a chance association only, it is due to excess tryptophan itself, or it is due to a combination of the impurity and excess tryptophan. A similar impurity has recently been identified in 5-HTP. The significance of this is also unknown.'

Among the conclusions:

> 'A further issue complicating use of 5-HTP and tryptophan is the type of preparation and dose. Trials evaluated used widely varying doses and dosage schedules. No consensus about appropriate dosage and frequency of administration exists to guide the clinician's prescribing.'

They conclude:

> 'Results of this meta-analysis are inconclusive due to the small number of sufficiently rigorous studies available on which to base conclusions. It is therefore difficult to recommend or discourage the use of 5-HTP and tryptophan in treatment of unipolar depression. More evidence is clearly needed to assess efficacy. Although the order of magnitude of effectiveness of 5-HTP and tryptophan was found in this study to be similar to selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCADs), the body of evidence evaluating the efficacy and safety of SSRIs and TCADs is more rigorous and comprehensive (Trindade and Menon 1997). Also, the relative potency of SSRIs and TCADs is possibly much greater, even though order of effectiveness is comparable. In settings where depression is mild, and the use of traditional antidepressants is unacceptable to the patient, tryptophan and 5-HTP may be considered as treatment alternatives… The possible link between tryptophan and 5-HTP and a potentially fatal side-effect makes their clinical use less appealing until this issue is resolved, particularly

> due to the availability of other antidepressants with proven efficacy and safety.'

In contrast to this conservative evaluation, the following advertisement appears on a web site that is easily accessible to consumers[28].

> 'Our isolated, singular, L-Crystalline Amino Acid L Tryptophan is made from organic crystals grown by a unique organic fermentation process very similar to that used by most vitamin manufacturers. No Animal products are used at any time. Even the capsules are vegetarian based and Kosher. All of our Nutraceutical Nutritional Products meet the highest USP and Pure Grade standards, require no digestion, and are completely non-allergenic. This product is listed in the Physicians Desk Reference PDR 2002. Most Other Companies Amino Acids, Vitamins, Mineral and Antioxidants are Food or Feed Grade.
>
> These amino acids have been validated in thousands of clinical trials and supported by "good science".'

## Anxiety, sedative effects

### *Kava*

Kava is another popular and widely used herbal preparation for which evidence and recommendations for usage are not easy to summarize. Although widely used for its purported anxiolytic effects, there have been recent cautionary warnings as well as controversy regarding these warnings.

According to a summary by Ernst[29], this Pacific Island plant, *Piper methysticum Forst.* (Piperaceae) has been used in the South Pacific for a variety of recreational and therapeutic reasons. The preparation has been used to facilitate smoking cessation (when combined with village group empowerment and ceremonies) and other conditions such as gonorrhea, syphilis, cystitis, sleep induction and weight reduction. There have been reports of mental and physical relaxant effects, and improvement in schizophrenic and mood disorders, resembling the effects of antipsychotics. There have also been reports of substance abuse in which kava is reputed to bring about a 'natural high'. In 1990, the German Commission E issued a statement supporting the use of kava pyrones (60–120 mg) for self-medication for up to 3 months. The relationship of kava to γ-aminobutyric acid (GABA) receptors in the hippocampus and amygdala complex, as well as dopamine D2 and histamine receptors has been described. Ernst has reported that 'An estimated 70 million daily doses have been consumed in Germany alone, although 70% to 80% of kava is consumed in Polynesia. In the USA, the total retail sale of kava was estimated at $17 millionin 1998.'

Another thorough review from the point of view of ethnopharmacology can be found in the article by Singh[30].

However, there have been reports of negative side-effects that may be associated with the use of kava[31]. Liver toxicity has been reported in several countries. Causality has been difficult to determine but, in the USA, health authorities have alerted consumers and

healthcare professionals to the risk of severe liver injury associated with kava. The allegation of harmful side-effects has been challenged as an example of negative bias towards herbal products. Those holding this view state that the risk/ benefit ratio and adverse reactions of kava compared to conventional anxiolytics has not been fully established. A report from the European Herbal Practitioners Association stated that many of the adverse events should not be attributed to kava. It also stated that concentrated standardized kava extracts—as opposed to preparations that closely approximate those created for traditional use—contribute to causing adverse events[32].

There is one report of Parkinsonism being associated with kava use in a 45-year-old woman with a family history of tremor. The symptoms were relieved by anticholinergics. The full causal relationship remains to be determined; however, the incident is added to the cautionary notes regarding kava[33].

The treatment effects of kava have been investigated in several trials[34]. One review concluded that kava products may be beneficial in the management of anxiety and tension of non-psychotic origin and do not adversely affect cognitive function, mental acuity or coordination in comparison with oxazepam. However, the report also noted that long-term use at higher doses (400 mg of kavalactones) may result in dermatitis with scaling on the extremities. While kava may potentiate the effects of other centrally mediated agents and interact with alcohol, few adverse effects were seen in a placebo-controlled, double-blind trial.

In one double-blind study, patients with agoraphobia, generalized anxiety and various other conditions were given either 90–110 mg of dry kava extract or a placebo for 25 weeks. The findings indicated significant improvement on standardized tests and a lack of drug tolerance[35]. Another small sample study examined whether the herbal anxiolytic kava, compared to placebo, produced improvement in vagal control in generalized anxiety disorder. The authors concluded that the preliminary findings suggested that kava might exert a favorable effect on reflex vagal control of heart rate in patients with generalized anxiety disorder[36].

Dosage recommendations range from a daily dose of 140–250 mg of standardized kava extract two or three times a day, to the German drug-regulating agency Commission E recommendation of about 200–400 mg a day. As with other anxiolytics, patients are warned about driving or operating heavy equipment. Kava is also contraindicated for pregnant or nursing women and for those with clinical depression or those who are using the herbs St John's wort or valerian. One case study also suggested that kava can interact with the anxiolytic drug alprazolam (Xanax®), causing lethargy and disorientation.

Pittler and Ernst provided a recent *Cochrane Database Systematic Review* regarding kava extract for treating anxiety[37]. Of the seven trials that met the inclusion criteria, all of the reviewed trials suggested superiority of kava extract over placebo. Three studies using the Hamilton Anxiety Score suggested a significant differential treatment effect in favor of kava extract. Adverse events as reported in the reviewed trials were mild, transient and infrequent. The authors concluded that the evidence implied that kava extract is superior compared with placebo and relatively safe as a treatment option for anxiety. They concluded with the usual caveat regarding the necessity for further and more rigorous investigations into the efficacy and safety of kava extract.

### *Lemon balm*

There is only preliminary research information concerning the use of lemon balm (*Melissa officinalis L.*, Lamiaceae) for its claimed anxiolytic effects. Six flavonoids have been isolated from the leaves of lemon balm[38]. One review concluded that no clinical studies supported its use and that no negative side-effects have been reported, but warned of the use with regard to pregnancy and lactation and potential interaction effects with other central nervous system (CNS) depressants (including alcohol) and thyroid medications or thyroid disease[39].

On the other hand, in a double-blind placebo-controlled study of lemon balm as a treatment for the management of agitation in severe dementia, 72 patients were randomly assigned to aromatherapy with *Melissa* essential oil or placebo[40]. The active oil and placebo were combined with a base lotion and applied to patients' faces and arms twice a day for a 4week period. Significant reduction in an agitation measure, a quality of life measure and percentage time engaged in constructive activities favored the essential oil treatment. No significant side-effects were observed. Basically, lemon balm has not been thoroughly evaluated but may have some favorable effects that would attract consumers to its use.

### *Skullcap*

A recent review concluded that the active ingredients and pharmacology of skullcap *(Scutellaria laterifolia L)* are not well documented, and the existing research may not apply to the preparations currently in use as a sedative and anticonvulsant[39]. Giddiness, confusion, sedation and seizures were potential adverse effects. The authors advised avoiding skullcap use in pregnancy and lactation and caution that there may be interaction with other CNS drugs.

### *Valerian*

The major reviews concerning valerian are in general agreement regarding the herbal preparation, its composition and the overall impression of the available research. Plushner's review contains a discussion of the pharmacology and purported mechanisms of action[41]. The general description states:

> 'Valerian is the common name given to the genus *Valeriana*, a perennial herb indigenous to many parts of North America, Europe, and Asia. Of approximately 200 known species, *Valeriana officinalis* is the one most commonly used for medicinal purposes. Medicinal uses for valerian date back to Hippocrates and include treatment of digestive problems, flatulence, and urinarytract disorders. The use of valerian to treat insomnia and nervous conditions began in the late sixteenth century and was firmly established by the eighteenth century. Valerian has been purported to be useful as a sedative-hypnotic, anxiolytic, antispasmodic, antidepressant, and anticonvulsant… Valerian preparations are commonly standardized

> according to their valepotriate content, which may range from 0.5% to 8% among valerian species. While valepotriates are acknowledged to have sedative-hypnotic effects, two controlled clinical studies confirming the efficacy of valerian in sleep disorders involved preparations with little or no valepotriates.'

Plushner cited studies indicating that biochemical receptor assays have demonstrated interaction with the inhibitory neurotransmitter GABA. Several research reviews support its use as a calmative and sleep-promoting agent. Overdose case reports include one patient who ingested 20 times the recommended therapeutic dose. The symptoms were mild and resolved within 24 h. Another study concerned an overdose of a sleep-inducing preparation that included valerian. Reports of hepatotoxicity were considered inconclusive, because of the multiple components of the suspected preparation. Longer-term studies were recommended to establish the risk for long-term users[42]. There are case reports of withdrawal symptoms associated with long-term, high-dose valerian, similar to those of sedative withdrawal[39].

In controlled trials, 400–900 mg of valerian extract has shown significant sedative effects. Some studies report effects that are comparable to those of benzodiazepines. Reported sideeffects included headaches, excitability, cardiac disturbances, drowsiness, blurred vision and restlessness.

There is consensus among the reviews that several clinical trials have been performed in humans to assess its sedative effects and found it to be effective in the treatment of mild-tomoderate sleeping disorders and states of restlessness and tension.

There is also consensus regarding the quality of the research on valerian. Generally, the interpretation of clinical studies of valerian is difficult, because of small sample sizes, suboptimal study designs, short treatment duration, lack of clear-cut inclusion and exclusion criteria, the heterogeneity of the study population, inconsistent or unknown valerian extract composition and failure to report potentially confounding variables such as use of other factors that influence sleep, treatment and measurement blinding, and use of different valerian preparations and outcome measurements. These differences among studies have made meta-analyses difficult, and only limited conclusions can be drawn regarding studies comparing valerian extracts with benzodiazepines.

The reviews include several cautionary notes. Valerian's sedative effects may be additive to those of other CNS depressants, and caution should be used when driving and in other situations requiring mental alertness. Valerian has not been demonstrated to be superior to existing hypnotic treatments or other treatments of insomnia. There is insufficient information to recommend valerian in pregnancy and during lactation. Valerian may potentiate the effects of other CNS depressants and the usual precautions taken with other sedating agents also apply to valerian. Valerian should be stopped about 1 week before surgery, because it may interact with anesthesia[43].

### *Passion flower*

Passion flower is derived from the dried flowering and fruiting top of a perennial climbing vine, *Passiflora incarnata L.* In spite of its popularity in Britain, it is a relatively unproven minor tranquilizer. The active component of passion flower is unknown.

Animal research has indicated prolonged sleeping time and reduction in amphetamine-induced hypermotility. Synergism with kava administration was also noted. The German Commission E has authorized its use in the treatment of nervous unrest, based on the results of animal research. Recent summaries are in general agreement regarding concerns about passion flower. Hypersensitivity, vasculitis and 'altered consciousness' have been reported with products containing passion flower. Interactions with other psychotropic medications have not been adequately studied. Because of its potential sedative effects, the usual precautions regarding operating motor vehicles or machinery should be made. Excessive use during pregnancy and lactation should be avoided. Because it is not regulated by the FDA, this product may be contaminated with other botanicals and/or the concentration listed on the label may be inaccurate[39,44].

Possible application to substance abuse treatment was shown in a study of 65 DSM IV defined opioid-dependent addiction patients randomly assigned to treatment with passiflora extract plus clonidine tablet or clonidine tablet plus placebo during a 14-day double-blind clinical trial. The passiflora plus clonidine group showed a significant superiority over clonidine alone in the management of mental symptoms associated with opiate withdrawal[45].

The effectiveness of *Passiflora* was compared to oxazepam in a study of 36 out-patients with generalized anxiety disorder using DSM IV criteria. Dosages for the two randomly assigned groups of patients were *Passiflora* extract 45 drops/day plus placebo tablet, and oxazepam 30mg/day plus placebo drops for a 4-week trial. The authors concluded that *Passiflora* extract may be an effective drug for the management of generalized anxiety disorder, and that *Passiflora* extract had a lower incidence of impairment of job performance. Given its popularity, larger-scale comparative and placebo controlled studies are indicated[46].

### *German chamomile*

This herb *(Matricaria recutita L)* has a mild hypnotic effect, and has been used in a variety of conditions: gastrointestinal, mouth and skin irritation, pediatric colic and teething, and mild insomnia and anxiety. There have been no randomized or controlled clinical studies. Adverse reactions are rare and mainly allergic in nature[39] .

### *Hops*

The female flowers of the plant *Humulus lupulus L* have been used as mild sedative and hypnotic agents. Hops used for flavoring in the manufacture of beer are only one of many ingredients selected for their contribution to flavor and intoxicating characteristics. There are no clinical studies of its effects as a single agent on insomnia or anxiety disorders. One review cautioned against its use in depression, in pregnancy and during lactation. Although there are currently no documented case examples, possible potentiation effects may exist when it is used with sedative hypnotic agents and alcohol[39].

## Eye movement

While each of the condition-specific treatments in this section are herbal preparations, there is one prominent and well promoted behavioral treatment that is specific to post-traumatic stress disorder and anxiety. Eye movement desensitization and reprocessing (EMDR) is a method discovered by F.Shapiro who reported reduced levels of distress associated with traumatic memories if the recall of these memories could be accompanied by a certain form of rapid and rhythmic eye movements. The treatment has its advocates and special training has been recommended in order to perform the treatment correctly. There is dispute regarding the nature of the research supporting the effectiveness of the treatment and the determination of the essential components of the treatment. It is generally conceded that the procedure is useful in the treatment of traumatic stress reactions for some patients. Criticisms generally concern the fidelity to standards of the treatment; the necessity of eye movements; the use of appropriate control groups, research designs and measures; consideration of co-morbidity; and consideration of other concurrent treatment. One of the topics of dispute concerns the assertion that, as the quality of the research increases, there is less support for the efficacy of the technique beyond its imaginal exposure component. A variety of initial reports and demonstrations have provided results, additional research has been recommended[47]. The method has developed a strong following of advocates, and national and international training courses are offered. The Cochrane Collaboration Depression, Anxiety and Neurosis Group is currently conducting a review of psychological treatments of post-traumatic stress disorder that will include the most commonly used treatments including EMDR[48].

## Schizophrenia

### *Evening primrose oil*

The oil of evening primrose *(Oenothera biennis L)* contains two essential fatty acids—linoleic acid and γ-linolenic acid. Linoleic acid is needed for the synthesis of prostaglandin E, and γ-linolenic acid is needed for the synthesis of prostaglandin $E_1$. The plant was used traditionally for medicinal purposes by the Native Americans and later became popular in Europe. Early clinical trials have investigated a variety of medical conditions including premenstrual syndrome (PMS) and schizophrenia. Reported side-effects include occasional nausea, indigestion and headache. Less common side-effects, including a potential risk of inflammation, thrombosis and immunosuppression, with prolonged use of γ-linolenic acid have been described.

There are conflicting reports concerning the effectiveness and side-effects of evening primrose oil. One small sample ($n$=13) in a double-blind crossover study found no significant therapeutic effect, but the authors discussed the possibility that the evening primrose oil strategy potentiates the epileptogenic properties of the phenothiazines[49]. Current reviews conclude that there is little evidence to support the use of evening primrose oil for psychiatric conditions such as schizophrenia, childhood hyperactivity and dementia. There are case reports indicating potential harmful effects in mania and

epilepsy. Phenothiazines, non-steroidal anti-inflammatory drugs, corticosteroids, β-blockers, and anticoagulants may interact adversely with evening primrose oil[39,50].

The Cochrane Collaborative Schizophrenia Group concluded that, while data were preliminary, results looked encouraging for polyunsaturated fatty acid (fish or evening primrose oil) for schizophrenia. There were no harmful effects reported in these studies, the products may be acceptable to people with schizophrenia and they may have a moderately positive effect. A further trial was soon to be reported from the USA and more were underway or planned in South Africa and Norway[51].

## Substance abuse

### *Kudzu*

Substance abuse is a vastly complex topic, because it includes a wide variety of substances, degrees of addiction, age and gender considerations, and cultural definitions and attitudes. There are several herbal preparations that are considered to be potentially useful, however. One that has received a great deal of attention is kudzu, *(Pueraria lobata),* a Chinese herbal medicine that has been used historically in the treatment of alcohol intoxication and is still prescribed in China and Southeast Asia. Puerarin, daidzin and daidzein, extracted from kudzu and given orally, suppressed voluntary alcohol consumption by alcohol-preferring P rats. Daidzin and daidzein were shown to be the active herbal components isolated from radix *Pueraria* (kudzu root) that suppressed alcohol intake in Syrian golden hamsters. Daidzin differs from disulfiram in its selective and reversible inhibition of aldehyde dehydrogenase class-1 (ALDH-1). Daidzin also decreases blood alcohol levels and shortens sleep time induced by ethanol[52,53]. However, it is difficult to compare the carefully controlled animal research with the common use by humans. The ingredients of kudzu are influenced by the geographical location of harvest, time of harvest, possible contaminants and uncertain quality control, so that, as with many herbal preparations, the consumer has little assurance of the exact ingredients and concentrations of the preparations currently available. From the clinical neurological point of view it would be important to know whether a patient is attempting to control drinking behavior with these preparations. Their sideeffects and interaction with other commonly used medications have not been established[54].

## Sexual dysfunction

### *Ginkgo biloba*

The *Ginkgo* tree has bilobed leaves which are similar to the maidenhair fern. It is believed to be the oldest living seed plant. Ginkgolic acid and related alkylphenols constitute major components of the lipid fraction of the fruit pods of *Ginkgo biloba L.* This class of substances is present in *Ginkgo* leaves which are widely used to prepare extracts for the treatment of peripheral or cerebral circulatory disorders, as well as vascular and Alzheimer-type dementia. Ginkgo is widely used in European medical practice to improve cognitive function in patients diagnosed with symptoms of ‘cerebral

insufficiency', with over 5 million prescriptions being written annually in Germany alone. Most of the clinical trials have used *Ginkgo* leaf extract EGb 761 (Tavonin™).

There is controversy regarding the use of ginkgo for the treatment of sexual dysfunction, primarily because of the inadequacy of the research. An open trial of *Ginkgo biloba* found significant improvement in antidepressantinduced sexual dysfunction predominantly caused by selective serotonin reuptake inhibitors (SSRIs), with women being more responsive to the sexually enhancing effects than men. It should be noted that this was a preliminary open-trial study[55]. On the other hand, no difference was found between ginkgo and placebo in a randomized placebo-controlled double-blind study[56]. Balon offered a critique of the studies dealing with antidepressant-induced sexual dysfunction[57]. Wong and colleagues[39] described an open-trial study of patients with proved arterial erectile dysfunction who had not previously responded to papaverine and who ingested 60 mg of *Ginkgo biloba* extract daily for 12–18 months. Fifty per cent of the men had gained potency after 6 months of therapy; however, the role of ginkgo in this recovery is difficult to determine, given the large psychological component of impotence and the fact that this trial was not blinded.

The most common side-effect is headache, which can be avoided by individualized graduated dosage. While concern has been expressed that ginkgo may potentiate other anticoagulants or increase bleeding time, the concern has not been substantiated. Generally, reviews conclude that caution should be exercised when ginkgo is combined with anticoagulant treatment, including aspirin, where there is a risk of bleeding as in peptic ulcer disease and subdural hematoma. Safety in pregnancy and lactation has not been established[39]. The Sloan-Kettering web site recommends the discontinuance of *Ginkgo biloba* at least 36 h before surgery. The web site indicates the existence of case reports of seizures in patients predisposed to seizures or on medications that lower the seizure threshold (e.g. prochlorperazine, chlorpromazine, perphenazine, etc.) and reports that spontaneous bleeding, including hematomas and hyphema, have been noted in the literature[58].

### *Siberian ginseng*

Siberian ginseng is believed to help fatigue and stress, to improve endurance and to have immunostimulatory properties. It is mentioned here because some studies report alteration of barbiturate-induced sleeping time by Siberian ginseng, and therefore should it be used with caution with sedative-hypnotic agents.

### *Ginseng*

There are several forms of ginseng in use at this time. Siberian ginseng *(Eleuthercoccus senticosus (Rupr* and *Maxim))* can be confused with plants of the genus *Panax* that include *Panax ginseng CA Meyer* (i.e. ginseng, Chinese ginseng, Korean ginseng) and *Panax quinquefolius L* (i.e. Canadian ginseng, American ginseng). Ginseng products are commonly used in the belief that they can treat stress and fatigue and improve endurance and other performance. The herb has received considerable research attention. The review by Wong and colleagues concluded that common side-effects include insomnia, hypertension, diarrhea, restlessness, anxiety and euphoria. The authors recommended

caution with regard to use in patients with hypertension and diabetes and in conjunction with centrally acting medications. They also noted that ginseng may potentiate the effect of monoamine oxidase (MAO) inhibitors, stimulants and haloperidol[39].

A recent review of adverse effects and drug interactions concluded that

> 'Combination products containing ginseng as one of several constituents have been associated with serious adverse events and even fatalities. Interpretation of these cases is difficult as ingredients other than *P.ginseng* may have caused the problems. Possible drug interactions have been reported between *P.ginseng* and warfarin, phenelzine and alcohol. Collectively, these data suggest that *P.ginseng* monopreparations are rarely associated with adverse events or drug interactions. The ones that are documented are usually mild and transient. Combined preparations are more often associated with such events but causal attribution is usually not possible.'[59]

A review of the use of ginseng in the treatment of sexual dysfunction—a common use in Asia—included the following major findings. Animal studies have shown support for the use of ginseng in the treatment of sexual dysfunction and provide evidence for a role of nitric oxide in the mechanism of ginsenoside action. Both Asian and American forms of ginseng enhanced libido and copulatory performance in laboratory animal studies. These effects are presumed to be due to ginsenoside actions on the CNS and gonadal tissues. The effects of ginseng on the corpus cavernosum appear to be mediated by the release and/or modification of the release of nitric oxide from endothelial cells and perivascular nerves. American ginseng has been shown to affect the activity of hypothalamic catecholamines involved in the facilitation of copulatory behavior and hormone secretion[60,61].

A recent study of 45 human subjects with clinically diagnosed erectile dysfunction examined the efficacy of Korean red ginseng for erectile dysfunction. The research design included a double-blind, placebo-controlled, crossover study (8 weeks on treatment, 2 weeks of washout and 8 weeks on treatment) in which the effects of Korean red ginseng and a vehicle placebo were compared using multiple variables. The ginseng dose was 900 mg three times daily. Erectile function scores and other measures were significantly higher in patients treated with Korean red ginseng than in those receiving placebo[62].

As with many of the herbal preparations described in this chapter, research reports can vary depending on the ginsenoside content of ginseng root or root extracts, the method of extraction, subsequent treatment and perhaps the season of its collection.

An example of ginseng products readily available in grocery stores is a form of ginseng tea (Ginseng Energy™) advertised as a combination of Asian and American ginseng with eleuthero root, B vitamins, chamomile, orange peel and spearmint leaves along with other ingredients. The warning regarding use is impressive, but in very small print. 'One should consult with one's health-care provider if also using prescription medication, or is pregnant or nursing. Persons with hypertension should avoid products containing eleuthero. Exceeding recommended dose may cause side-effects such as anxiety, breast pain, fever, headache, hypertension, insomnia, irritability, menstrual

changes, nervousness, pruritus, sexual dysfunction, and vertigo.' The warning indicates responsible product description, but users who do not follow directions may present interesting clinical pictures, especially considering the evidence that many patients do not discuss their use of CAM products with their physicians and may be using them in addition to prescribed medications. Furthermore, of course, the actual dosage could vary considerably depending on how the tea was prepared.

### *Yohimbine*

Yohimbine is an indole alkaloid obtained mainly from the bark of the yohimbe tree *(Pausinystalia yohimba)*, a common tree in West Africa. It is an $\alpha_2$-adrenoceptor antagonist that is marketed pharmaceutically for treatment of impotence. The reviews regarding its use fall into two different categories, one favoring its use and the other warning of potential major side-effects. Meta-analyses have been conducted regarding studies of the preparation's effectiveness for sexual dysfunction. One metaanalysis of randomized, placebo-controlled trials of yohimbine monotherapy for erectile dysfunction concluded that yohimbine is superior to placebo and that serious adverse reactions were infrequent and reversible. The authors cited evidence that no single serious adverse effect had been reported in any clinical study conducted to that date. However, the authors cautioned that

> 'the drug is not free of adverse effects. In particular those adverse effects relating to cardiovascular conditions are relevant since populations suffering from erectile dysfunction have a high incidence of cardiovascular disease. As with many dietary supplements, the actual amounts of yohimbine can vary considerably.'[63]

Early studies range from small sample case studies to a retrospective study of 45 patients self-selected from a pool of 97 having sexual dysfunction associated with SSRIs. The study compared yohimbine, amantadine and cyprohepatidine, and found that all three antidotes were safe and relatively effective, although yohimbine was significantly more effective in reversing SSRI-induced sexual dysfunction. Given the sampling and design of these studies the results are clearly preliminary[64].

Several studies have used a variety of animal models. For example, yohimbine has been demonstrated to enhance sexual behaviors in male rats, including those that have been castrated, or in aging male rats[65].

One reviewer decried the lack of properly designed human trials of yohimbine given the positive findings in animal and human research. According to this author alternative routes of administration, dose response, continuous versus on-demand administration, synergism with other drugs, and other features should be tried[66].

There are several warnings regarding the use of yohimbine. One study reported the effects of yohimbine on blood pressure and plasma levels of catechols in patients with essential hypertension. The study concluded that yohimbine stimulates sympathetically mediated plasma norepinephrine (noradrenaline) levels and that the increased levels produce a pressor response. The authors stated that

> ‘yohimbine should be administered with caution to patients with high blood pressure, especially in individuals with evidence for increased basal sympathetic outflow or those undergoing concurrent treatment with tricyclic antidepressants or other drugs that interfere with neuronal uptake or metabolism of norepinephrine.’[67]

Another major concern is the potential for the production of psychopathology. The authors of this review reported that yohimbine is commonly used to provoke panic attacks and anxiety in studies of the pathophysiology, psychopharmacology and treatment of anxiety disorders. They pointed out that tricyclic antidepressants, medications with central α-adrenergic blocking properties, centrally acting sympathomimetics, MAO inhibitors and antimuscarinic agents potentiate the action of yohimbine. They conclude their summary with cautionary statements that stress the potential of yohimbine to produce psychiatric symptoms, primarily anxiety or panic, especially in patients with pre-existing panic disorder. However, they point out that many commercial products derived from yohimbe bark contain little or no actual yohimbine[39].

## TREATMENTS AND SYSTEMS ADDRESSING MULTIPLE CONDITIONS

While the above-described preparations tend to be associated with a particular form of psychiatric problem, there are many other preparations and systems of medicine that claim relevance to several problems or conditions.

### Acupuncture and acupressure

Over the years, the United States Public Health Service (NIH and particularly the former ADAMHA Institutes) has funded a variety of research projects on acupuncture, including studies on the mechanisms by which acupunc-ture may have its effects, as well as clinical trials and other studies. There is also a considerable body of international literature on the risks and benefits of acupuncture, and the World Health Organization lists a variety of medical conditions that may benefit from the use of acupuncture or moxibustion. Such applications include prevention and treatment of nausea and vomiting; treatment of pain and addictions to alcohol and illicit drugs; treatment of pulmonary problems such as asthma and bronchitis; and rehabilitation from neurologic damage such as that caused by stroke. A recent NIH Consensus report does not include reference to psychiatric conditions other than addiction. There are several indications, however, that acupuncture practitioners may consider the method to be effective for emotional problems and distress[68].

In the process of reviewing research find-ings on acupuncture a variety of practices were found to be included under the term ‘acupuncture’, e.g. auricular (ear) acupuncture, wholebody acupuncture, non-specific acupuncture, electroacupuncture, aquapuncture, acupuncture combinations of locations and depth of insertion, those with and without twirling of the needles, combinations of acupuncture with other forms of CAM and with other forms of conventional therapy and medications. In taking a patient’s medical

history it is important to elicit the details of actual practice and not assume that a common terminology exists among practitioners and the general public.

### *Depression*

Although preliminary research studies illustrate the early support for the use of acupuncture in the treatment of depression, the studies are clinical observation studies. However, there are studies conducted in Germany, Russia and the USA that used placebo and noacupuncture controls, pharmacological comparison groups and measures commonly employed in Western research on depression.

In a study of 70 patients, a comparison was carried out of whole-body acupuncture to nonspecific acupuncture as adjuvants to the antidepressant mianserin plus clinical management. The authors concluded that those receiving acupuncture improved slightly more that those receiving the antidepressant alone[69].

A study of body needle acupuncture in 43 patients with minor depression and 13 with generalized anxiety used a placebo-controlled, randomized, modified double-blind design. The authors concluded that, after ten acupuncture treatments, those receiving acupuncture responded with significant clinical reduction in anxiety symptoms in minor depression or generalized anxiety[70].

The authors of a study investigating the use of acupuncture with 72 manic-depressive and 95 schizophrenic patients concluded that 'the effectiveness of acupuncture was inferior to tricyclic antidepressants in patients with psychotic depression, but was almost as effective as antidepressants in cyclothymic depressions.'[71] Six of 38 patients resistant to antidepressants 'showed considerable and lasting improvement or complete remission from depression following a course of acupuncture. For most of the other subjects, acupuncture increased sensitivity to subsequent drug therapy and shortened the period of treatment.'

A 1984 report from Taiwan, appearing in *Biological Psychiatry,* suggested that electroacupuncture using a low-voltage apparatus may be safer than standard electroshock therapy (ECT) for antidepressant non-responders with ECT contraindications[72].

The overall status of acupuncture in the treatment of depression is inconclusive. There is great variety of sample composition and sample size, type of treatment, research design and outcome measures. The 1998 review cited above had classified acupuncture as well as relaxation as having 'lesser extent' of benefits and requiring further randomized controlled trials[10].

However, placebo factors may be particularly pertinent to investigations of complementary therapies such as acupuncture, where experimental blinding of treatment is especially difficult and controversial. The Cochrane Review of placebo-controlled studies of depression concluded that

> 'Although there is a consensus that antidepressants are effective in depression, placebo effects are also thought to be substantial. Side effects of antidepressants may reveal the identity of medication to participants or investigators and thus may bias the results of conventional trials using

> inert placebos. Using an "active" placebo which mimics some of the side effects of antidepressants may help to counteract this potential bias.'

The review concluded:

> 'The more conservative estimates from the present analysis found that differences between antidepressants and active placebos were small. This suggests that unblinding effects may inflate the efficacy of antidepressants in trials using inert placebos.'[73]

These unblinding effects also included attitudes and beliefs of the investigators and administrators of the treatments, factors that may be expected to be found in preliminary research on CAM treatments such as acupuncture.

### *Anxiety*

The calming, soothing, relaxing effects of acupuncture are commonly observed by acupuncturists, treatment program administrators and many recipients of the treatment. A demonstration study using healthy volunteers compared bilateral Shenmen acupuncture with the 'relaxation point' acupuncture and with a sham acupuncture point. Anxiety level was significantly less for the relaxation point group compared to the Shenmen group and to the sham acupuncture group[74].

### *Schizophrenia*

Summary of the research information regarding schizophrenia is especially difficult because of the variation in nomenclature, research design, measurement and treatment methods. For instance:

(1) A 1995 study conducted in Inner Mongolia concerned the treatment of schizophrenia with acu-moxibustion and Chinese medicine[75].
(2) One study ($n$=40) provided preliminary information that acupuncture might serve to reduce the dose of antipsychotic medication for schizophrenics, thereby reducing side-effects without reducing clinical effectiveness[76].
(3) A recent review of acupuncture for schizophrenia concluded that 'research on acupuncture or low-power laser treatment was significantly or seriously flawed. While some studies (eight papers were reviewed) suggest that the treatments may be as effective as chlorpromazine in schizophrenia, no scientifically sound conclusions can be drawn.'[77]

As with the treatment of depression, there may be an important placebo effect at work in the above studies. The Cochrane Schizophrenia Group review of chlorpromazine and placebo concluded that 'chlorpromazine is a well established but imperfect treatment' and that there was a 'humbling 40% improvement rate in those who were allocated to placebo'[78].

### *Substance abuse*

Recent studies and reviews do not provide support for the use of acupuncture in substance abuse, in particular alcohol, cocaine and nicotine. While early studies suggested that acupuncture might be associated with reduction in alcohol abuse, later studies by the same authors did not confirm these early findings. A largesample (*n*=503), single-blind, randomized placebo-controlled study found that three types of acupuncture did not make a significant contribution over and above that achieved by conventional treatment alone. The treatments compared were acupuncture points specific for substance abuse, non-specific acupuncture points, symptom-based acupuncture points, or conventional treatment alone. All patients received conventional treatment. The measures included alcohol use, depression, anxiety, functional status and preference for therapy. The conventional treatment was an intensive group and individualized treatment program typical of advanced treatment programs. The research did not address the use of acupuncture alone in the treatment of alcoholism because all individuals seeking treatment in Minnesota cannot be denied conventional treatment. Relevant to the popularity of acupuncture for substance abuse, patients receiving acupuncture perceived a benefit that they attributed to the treatment. To answer a frequent criticism of acupuncture research that the treatments are artificially and inappropriately restricted to specific locations, this research also used acupuncture based on the presenting symptoms of each patient, a procedure close to the actual clinical practice[79].

The treatment effect of acupuncture on cocaine use remains to be demonstrated. In a randomized, placebo-controlled research study of acupuncture and cocaine use, 165 of 435 (38%) patients completed treatment. Differences were not found among different doses of acupuncture, true and sham acupuncture, and standard treatment—consisting of an intensive, multi-component group and individual treatment program taking place in a day treatment and a residential program. Once again, patients receiving acupuncture perceived significant improvement. This perception of improvement was not related to a measure of placebo responsiveness[80].

Acupuncture treatment of cocaine addiction was investigated in a multi-site study in six community-based clinics in the USA—three hospital-affiliated clinics and three methadone maintenance programs. A total of 620 cocainedependent adult patients were treated; 412 used cocaine only and 208 used both opiates and cocaine and were receiving methadone maintenance. Patients were randomly assigned to receive auricular acupuncture, a needleinsertion control condition, or a relaxation control condition. Following current practice, treatments were offered five times weekly for 8 weeks. Concurrent drug counseling was also offered to all patients. Forty-five per cent of the assigned patients completed the full 8-week trial. Although methadone-maintained cocaine users were significantly more likely to complete treatment (63%) than were primary cocaine users (36%), there was no significant difference in the completion rate by treatment condition collapsed across sites. Analysis of urine samples showed a significant overall reduction in cocaine use but no differences by treatment condition. There were also no differences between the conditions in treatment retention (44–46% for the full 8 weeks)[81].

Throughout this chapter criticisms have been described regarding the artificial constraints on CAM treatments imposed for the purposes of research, restraints that distort the actual CAM practices. The alcohol study described above attempted to deal

with this problem by using the recommended National Acupuncture Detoxification Association (NADA) protocol and by including symptombased acupuncture, not restricted to the auricular ear points alone. The multi-site cocaine study used a four-needle treatment, while the standard NADA treatment typically involves five. The study treated patients in small groups or possibly alone, whereas in NADA clinics patients are more often treated in larger groups. The research did not integrate the study treatments within a comprehensive treatment program, as is recommended in the NADA literature. However, the authors concluded that they did not find acupuncture more effective than a needle insertion or relaxation control in reducing cocaine use. In addition they concluded that their findings did not support the use of acupuncture as a standalone treatment for cocaine addiction or when patients receive only minimal concurrent psychosocial treatments. They recommended further research regarding the contribution of acupuncture when provided in an ancillary role.

It is important to note that there is significant attrition in addiction research. In the two cocaine studies, less than half completed the treatment and about one-third of the initial sample completed the follow-up measurement. Higher rates of follow-up success were reported for the other measures, but the overall attrition rate remained a significant issue. While it is conceivable that reliable treatment differences could be detected under these circumstances, the attrition rates limit our full knowledge of potential treatment effects. While statistical methods can be used to adjust for missing data, the conservative judgement would be that the results can be generalized only to patients who complete treatment and follow-up visits.

The use of acupuncture in the treatment of smoking is another popular application that has been tested several times without demonstration of benefit. The research on this topic is often inconclusive because of the wide variation in the definition of the treatment and the variation in research methods.

The recent report by the Cochrane Tobacco Addiction Group summarized the research concerning acupuncture and related techniques as treatment for smoking cessation[82]. They reviewed randomized trials of acupunc-ture and the allied therapies of acupressure, laser therapy and electrostimulation, in comparison with: sham treatment; other interventions; or no intervention. The intervals at which they assessed abstinence were before 6 weeks, at 6 months and at 1 year or more. After reviewing 22 studies the authors concluded that acupuncture was not superior to sham acupuncture in smoking cessation at any time point. Similarly, when acupuncture was compared with other anti-smoking interventions, there were no differences in outcome at any time point, and only a temporary superiority to no intervention in the early results. Different acupuncture techniques did not show any one particular method (i.e. auricular acupuncture or non-auricular acupuncture) to be superior to control intervention. Their summative conclusion was that there is no clear evidence that acupuncture, acupressure, laser therapy or electrostimulation are effective for smoking cessation.

Physicians and other therapists who are aware of the research will face a dilemma when dealing with individuals who have experienced improvement or ‘cure’ of alcoholism or nicotine addiction and are convinced of the benefits of the CAM treatment, in this case acupuncture. Feelings in this area can run high, and the therapist runs the risk of discrediting a strongly held belief, implied ridicule, demoralization and perhaps resumption of the addiction (see the section on nocebo effects). The research does not say

that no one has ever benefited from these therapies, either directly or perhaps through a complex self-healing process that may be initiated by treatment participation.

### *Sexual dysfunction*

In an open trial report on the use of acupuncture for the treatment of psychogenic impotence, 20 out of 29 subjects demonstrated improvement[83]. This evidence is based on ca learly preliminary research design in an area having considerable placebo effects. However, the study does indicate that acupuncture has been and probably still is being used for sexual dysfunction. The 20 subjects experiencing improvement were probably convinced of the treatment's effectiveness.

## Aromatherapy

Aromatic commercial products such as bath preparations, perfumes, candles and lotions are popular as gifts and self-care products that should probably not be considered 'therapies' any more than morning coffee might be considered caffeine therapy—although moodaltering results may be forthcoming. Formal aromatherapy, the therapeutic use of aromatic plant oils, is one of the fastest growing alternative therapies in the USA and Europe. Aromatherapy was named by the French chemist René-Maurice Gattefosse in 1928. Substances with strong odors were used in ancient civilizations both as medicine and as perfume. Today, plant oils are inhaled using atomizers or absorbed though the skin during massage (aromatherapy message). Plant oils are said to have many therapeutic effects—analgesic, psychological and antimicrobial—some of which have been demonstrated in various ways. For instance, oil of cloves is a commonly used dental analgesic. Aromatherapy is said to relieve stress and anxiety and to alleviate gastrointestinal and musculoskeletal disorders, among others. In psychiatry, olfactory stimulation has been used to elicit feeling tones, memories and emotions during psychotherapy. The essential oils used in aromatherapy can cause skin irritation or allergic reactions in some people.

An example of aromatherapy research as it pertains to psychiatry is an open-trial, smallsample ($n$=15) study of depressed patients that was conducted in Japan. It was reported that the application of citrus fragrance could markedly reduce necessary doses of antidepressants[84]. While replication, larger samples and placebo controls would be required to substantiate this finding, the result is consistent with reports of users of aromatherapy. The authors referred to previous animal research indicating that citrus fragrance could alleviate stress-induced immunosuppression, and various scents have been used in nursing homes to improve the mood of severely demented (and other) patients.

The Cochrane Dementia and Cognitive Improvement Group is reviewing the available research to assess the efficacy of aromatherapy as a treatment for people with dementia[85].

## Flower essence therapy

A related method, Bach flower essence therapy, first described by British homeopath Edward Bach, involves the creation of elixirs produced by flowers floating in a bowl of

water in sunlight. These elixirs are consumed and practitioners claim that the treatment produces gentle healing and is free of negative side-effects. While there are anecdotal reports of the use of these modalities for the treatment of addictive disorders and post-traumatic stress disorder, efficacy remains to be demonstrated[86].

## Ayurveda

The Western physician may encounter patients who have in the past or are currently receiving some treatments derived from Asian Indian medicine, which has been traced to sacred writings dating to the 2nd millennium BC. This system of medicine evolved through early periods of magical practices and use of a wide variety of herbal medicines. Practitioners trained in both Western and ayurvedic medicine may combine treatments from both traditions depending on the condition or stage of condition, including prevention. Only careful history taking will discover the patient's particular herbal, dietary or other practices in addition to Western medical treatments. Medical treatises written during a period around the 1st century AD form the basis for most later writings. Current forms of this medical system demonstrate both Buddhist and Hindu contributions, and are highly respected, involving considerable medical training from recognized ayurvedic medical schools all over India.

Recent writings pertaining to psychiatry include treatises explaining achievements in the field of mental health, basic ayurvedic concepts and their relationship to the modern scientific world. Ayurvedic concepts may be related to conditions such as anxiety, neurosis and depressive disorders. Medical literature reviews have compared ayurvedic concepts to the works of Freud, Kurt Lewin's field theory, homeostatic imbalance as a source of mental illness, and personality types and their corre spondence to types of mental disorders[87].

Research evidence is difficult to summarize, since ayurveda is a system of medicine rather than a particular treatment. There may be relevant research on individual components but it should be remembered that these components are probably administered within a context of multiple treatments.

## Bioenergetics

Bioenergetic therapy may include a variety of psychotherapeutic and other treatments included under the banner of CAM. The treatments are based on the belief that damned-up 'vital' energy produces maladaptive behavioral patterns. The Austrian psychoanalyst Wilhelm Reich (1897–1957), who studied with Sigmund Freud, believed that energy fields were propelled by sexual impulses called ergs and that satisfactory orgasms were an indication of healthy bodily functioning. The emphasis on sexual energy has diminished and modern-day practitioners look for areas of muscular tension in the body that are thought to be associated with repressed memories and emotions. Therapists try to bring these repressions to consciousness through a variety of relaxation techniques, including massage or non-contact methods resembling Therapeutic Touch. The research published in this area includes topics such as the effects of bioenergetics and progressive relaxation on self-concept, locus of control and social behavior of hospitalized psychiatric patients.

Psychotherapeutic methods include the use of deep breathing and focusing on attendant bodily feelings, together with facilitated fantasy development. Four types of related body psychotherapies are Gestalt therapy, Reichian therapy, Lowenian bioenergetics and primal therapy. All share the belief that psychopathological functioning is rooted in rigidification of behavior and experience that are biologically and somatically, or physically remembered as opposed to reasoning of mental consciousness or CNS memory. There are several therapies that employ various kinds of mental and physical manipulations to 'dislodge' traumatic memories of painful events stored in physical locations of the body.

The shadow of disrepute that may linger over this field is derived from Reich's efforts to measure units of cosmic energy and to treat mental illness as a deficiency in this energy. Specially constructed cabinets called orgone boxes were leased as therapy for many illnesses including cancer. The treatment terminated as a result of legal action in the 1950s. The therapies evolving from Reich's early formulations are not related to this product.

## Biofeedback

Because of the readily available modern equipment for biofeedback, there are many self-declared practitioners of the method, but formal certification can be obtained from the Biofeedback Certification Institute of America. There is a huge literature pertaining to the physiological mechanisms of biofeedback and its application to a wide variety of medical and psychiatric conditions[88]. It would be wise to inquire about the professional background of therapists reported by patients as administering their biofeedback treatments.

Biofeedback is a therapeutic process in which information about an individual's physiological processes such as blood pressure, heart rate, electroencephalogram (EEG), temperature of extremities, or muscle tension is monitored electronically and 'fed back' by means of sounds, lights, or electronic gauges. It has been found that, using these techniques, individuals can learn to control a variety of physiological responses formerly thought to be completely involuntary, and thereby deal more effectively with stress reactions such as anxiety and pain. Feedback regarding EEG status has also been found to be useful—alpha waves being associated with relaxation and meditation, theta waves with focused attention. Herbert Benson has described a common 'relaxation response' visible in most people as a result of alpha wave biofeedback, transcendental meditation, or other reproducible meditation techniques[89].

There have been some early findings that alpha/theta feedback may have significant effects on substance abuse. Several studies have shown positive effects on pre-surgical anxiety. There are a sufficient number of studies to permit meta-analyses of various forms of anxietyreduction methods, including biofeedback. In substance abuse studies, the various therapeutic components of the biofeedback process have not been separated. Number of sessions, attention effects, relationship with the therapist and situational demand are some of the variables that could be involved in producing the treatment effects[90].

A review of biofeedback for mental disorders concluded that the method could help selected patients modify specific responses or response patterns, but it does not appear to be a treatment of choice for any mental disorder[91].

### Chiropractic

This system of therapy can contain many components, including herbal therapy. In taking a medical history it would be wise to inquire about the particular nature of chiropractic treatment received by a patient in order to determine compatibility with the planned treatment. There is little available research regarding chiropractic treatment of psychiatric illnesses. One small-sample ($n$=21) study of patients with elevated blood pressure involved randomization to active treatment, placebo treatment, or no treatment. Active treatment was found to be related to reduced blood pressure while state anxiety was reduced in the active and placebo treatment. This is an early preliminary study that could form the basis for more definitive studies[92].

### Dance therapy

The American Dance Therapy Association defines dance therapy as 'the psychotherapeutic use of movement which furthers the emotional and physical integration of the individual'. Dance therapy was formally recognized in 1942 at St Elizabeth's Hospital in Washington, DC. Although within the profession 'dance' and 'movement' are widely used synonymously, each term actually describes a point of view: movement encompasses the whole world of physical motion, whereas dance is a specific creative act within that world, usually involving music.

Dance therapy sessions have four basic goals: the development of body awareness; the expression of feelings; the fostering of interaction and communication; and the integration of the physical, emotional and social experiences that result in a sense of increased selfconfidence and contentment.

There are several hundred references to dance therapy, many of them descriptive and theoretical. The method has been applied to a wide range of psychiatric conditions. A metaanalysis of 23 studies, with a total sample of 781 subjects, concluded that dance and movement therapy could be effective for treatment of a variety of symptoms, particularly anxiety. However, the research was characterized as having methodological problems such as inadequate control groups and lack of use of standardized measures[93].

### Orthomolecular medicine

In addition to the well-accepted role of nutritional deficiencies on mental and physical functioning, in the early 1950s some psychiatric investigators emphasized the function of nutrition, including food allergies, vitamins, minerals and amino acids for the treatment of conditions such as schizophrenia, depression, anxiety, childhood hyperactivity and autism. The treatments are best known for their search for deficiencies or mal-utilization of vitamins and amino acids, and the prescription of large doses of vitamins, generally known as megavitamin therapy. The rectification of metabolic and nutritional deficiencies is believed to obviate the necessity for psychiatric medications and

ameliorate side-effects when standard treatment is required. The next section regarding omega-3 fatty acids is an example of orthomolecular theory and practice.

The general visibility and advocacy of this approach is attributed to the work of the Nobel laureate Linus Pauling, who in 1968 and in many subsequent publications put forth the general theory of orthomolecular (from the Greek word *ortho*, 'to correct') medicine. Pauling's early interest in molecular structures led in 1934 to the study of proteins in hemoglobin and in immunological reactions, and also amino acids and polypeptides. In 1973 he founded the Linus Pauling Institute of Science and Medicine to study the prevention and treatment of illness through the intake of optimum doses of vitamins and minerals, especially the daily intake of megadoses (6–18 g) of vitamin C recommended for the treatment of the common cold, cancer and aging.

A summary of Pauling's theory can be found in the title and abstract from his 1995 article, 'Orthomolecular psychiatry: varying the concentrations of substances normally present in the human body may control mental disease'[94].

> 'The functioning of the brain is affected by the molecular concentrations of many substances that are normally present in the brain. The optimum concentrations of these substances for a person may differ greatly from the concentrations provided by the normal diet and genetic machinery. Biochemical and genetic arguments support the idea that orthomolecular therapy, the provision for the individual person of the optimum concentrations of important normal constituents of the brain, may be the preferred treatment for many mentally ill patients. Mental symptoms of avitaminosis sometimes are observed long before any physical symptoms appear. It is likely that the brain is more sensitive to changes in concentration of vital substances than are other organs and tissues. More over, there is the possibility that for some persons the cerebrospinal concentration of a vital substance may be grossly low at the same time that the concentration in the blood and lymph is essentially normal. A physiological abnormality such as decreased permeability of the blood-brain barrier for the vital substance or increased rate of metabolism of the substance in the brain may lead to a cerebral deficiency and to a mental disease. Diseases of this sort may be called localized cerebral deficiency diseases. It is suggested that the genes responsible for abnormalities (deficiencies) in the concentration of vital substances in the brain may be responsible for increased penetrance of the postulated gene for schizophrenia, and that the so-called gene for schizophrenia may itself be a gene that leads to a localized cerebral deficiency in one or more vital substances.'

The field of orthomolecular medicine is characterized by the strongly held beliefs of advocates and the challenge by skeptics. Research has addressed the use of megadoses of vitamin $B_3$ in the form of niacin on schizophrenic patients sometimes combined with other nutrients and a high-protein diet. Anxiety is examined for its cause in abnormal glucose tolerance. Treatments of depression include amino acids and other necessary precursors for the production of norepinephrine and serotonin. Generally, this approach

to treatment is characterized by a carefully planned program to supply the body with the nutrients it needs to restore its own internal balance.

The research on these concepts has been criticized for limitations in design, sample size and varying conclusions. The Cochrane Collaborative summarized the efficacy of vitamin $B_6$ and magnesium in the treatment of autism in the following way:

> 'Several investigators have reported that autistic individuals showed significant improvement during vitamin $B_6$ (pyridoxine) and magnesium treatment. The dose of pyridoxine ranged from 15 to 30mg/kg per day or 700 to 1000mg/d; and the dose of magnesium ranged from 10 to 15 mg/kg per day or 380 to 500 mg/d. However, the treatment periods were rather short (2 weeks to 30 days), and the behavior scales used to evaluate the outcomes were not specific to autism. Other investigators have failed to confirm the positive findings. A review of this issue by Pfeiffer et al. concluded that even though the majority of studies report a favorable response, the interpretation of these findings needs to be tempered because of methodological shortcomings inherent in many of the studies.'[95]

Orthomolecular medicine continues to be an area of controversy with advocates and their *Journal of Orthomolecular Medicine,* and skeptics ready to challenge research findings. The variation in research topics and methodology will delay comprehensive meta-analytic summaries.

As with many of the CAM treatments described in this chapter, there is special concern regarding self-administered, non-supervised use of very large doses of vitamins and minerals. The symptoms and conditions can vary widely depending on the preparations used, their interaction with other treatments and the underlying self-diagnosed conditions that were the motivation for their use.

### *Omega-3 fatty acids*

A recent comprehensive review of omega-3 fatty acids describes the history of evidence regarding the function of certain essential fatty acids (EFAs) in fetal and neonatal development and hypotheses regarding deficiencies in dietary EFAs potentially leading to diseases such as multiple sclerosis, arthritis, enteritis, immune system dysfunction, heart disease, cancer, diabetes, schizophrenia and bipolar disorder[96]. The review provides the following background and rationale for the use of this treatment.

Linoleic acid (18:2n-6) and α-linolenic acid (18:3n-3) must be consumed in the diet because humans lack the ability to synthesize them. The author describes the phospholipid deficiency hypothesis linking food processing and dietary habits to an increased ratio of omega-6 to omega-3 fatty acids. The omega-6 fatty acids are crucial to synthesis of many cytokines that mediate inflammation, including several interleukins, tumor necrosis factor-α (TNF-α) and interferon-γ. In contrast, diets high in the omega-3 fatty acids are correlated with reduced overall production of these inflammatory cytokines.

Lake[96] describes the preliminary clinical and laboratory research and potential relationship to current pharmaceutical agents, with regard to Horrobin's membrane phospholipid model of schizophrenia. In this model abnormal metabolism of phospholipids resulting from genetic and environmental factors manifests as a range of symptoms that are classified as schizophrenia[97,98]. He also summarizes the correlation of information regarding crossnational rates of depression and dietary intake of omega-3 fatty acids as well as the application of the Horrobin model to laboratory and preliminary clinical studies of depression. Early promising findings regarding bipolar disorder led to a grant from the National Center for Complementary and Alternative Medicine to repeat an earlier study on a larger scale and with a more rigorous design using 120 patients. A multicenter study funded by the National Institute of Mental Health is underway on the effects of omega-3 fatty acids in the treatment of major depression and bipolar disorder.

Other early findings relate to the treatment of cognitive decline, violent and impulsive behavior, dyslexia and attention deficit hyperactivity disorder (ADHD).

According to the review, no significant safety issues are associated with consumption of unsaturated fatty acids, including EFAs, as long as these substances do not account for more than 10% of total caloric intake. Beyond that level a number of case studies have reported problems with glycemic control in diabetics, increased bleeding, potential problems in the metabolic clearance of certain medications, possible episodes of hypomania, increased incidence of hypertension and stroke. Some non-serious gastrointestinal complaints may be associated with significant fish oil dosages.

There are different perspectives on the effectiveness of omega-3 fatty acids in the treatment of schizophrenia. The review by Mahadik and colleagues provides an extensive rationale for probable effectiveness especially at or before the onset of psychosis[99]. On the other hand, Fenton and colleagues followed up on preliminary reports indicating symptom improvement ranging from 17% to 85% when omega-3 fatty acids were added to patients' usual medications[100]. The authors conducted a study using 3g/day of ethyl eicosapentaenoic acid (EPA) in a 16-week, double-blind, placebo-controlled trial involving 87 schizophrenia patients with clinically significant residual symptoms despite neuroleptic treatment. They concluded that improvement in residual symptoms and cognitive impairment was no greater than for schizophrenia patients treated with placebo. While stage of illness was not under investigation, outcome expectations for patients resistant to standard therapy were delineated.

A particularly helpful reference site regarding omega-3 that summarizes pharmaceutical and clinical information has been provided by the Linus Pauling Institute Micronutrient Information Center[101].

## Transcranial neuroelectric stimulation

This is a relatively unknown treatment originally used in the 1950s for the treatment of depression, anxiety and substance abuse detoxification. The typical application of this method involves the placement of surface electrodes in the mastoid region. The electrodes are stimulated using low amperage and frequency of alternating current. No seizures are induced and the treatment should not be confused with ECT. Studies of the effectiveness of this method on treatment of substance abuse have not shown a consistent

treatment effect, although greater comfort during detoxification has been reported. Similar methods have been called Limoge and Russian Electrosleep therapy.

An example of its use in substance abuse research was published in 1992[102]. Neuroelectric therapy (NET) was tested in a doubleblind, randomized, placebo-controlled study in the treatment of withdrawal and stabilization of 18 opiate-dependent and 25 cocainedependent subjects. Both cocaine and opiate groups reported a comfortable detoxification and substantial improvement over the course of a 12-day hospitalization. There was no significant difference between the active or placebo groups, suggesting that placebo was as effective as active NET in reducing drug withdrawal or craving during cocaine and opiate detoxification. However, all placebo patients received 0.2 mA of current, which may have provided some degree of active effect.

A related method called rapid-rate transcranial magnetic stimulation (rTMS) applies electromagnetic stimulation. There are several reviews of the research in this area, which is generally characterized as preliminary. A recent review of the evidence for rTMS reviewed all published evidence and identified only 12 studies that met their predetermined criteria for inclusion[103]. The treatment administration varied widely, as did patient characteristics. The authors concluded that more, larger and more carefully designed studies are needed for a convincing demonstration of a clinically relevant effect of rTMS, and that there is insufficient evidence for rTMS as a valid treatment for depression at present.

The research is clearly in a preliminary state, primarily in the form of demonstration research. The effectiveness and side-effects have not been established.

## Homeopathy

The full description of homeopathy and its history is presented elsewhere in this textbook (see Chapter 7). In addition, a thorough description and review has been provided by Vickers and Zollman[104]. In spite of its controversial relationship with conventional medicine, the practice of homeopathy is increasing in the USA and around the world. In Europe, homeopathy has been popular throughout the 20th century, and in India it has retained its enormous popularity since introduction by the British Empire. Homeopathic medicines are sold over the counter in the USA.

The homeopathic process begins with administering small doses of a substance to healthy volunteers to determine the agent's symptom profile. This is called a homeopathic 'proving'. A substance would be chosen for a patient by giving the patient the substance that had a symptom profile most closely matching the patient's symptom profile. Classical homeopathy develops individualized treatment for each patient; however, there are a variety of other approaches. Homeopathic remedies sold in the USA must meet the standards of monographs in the Homeopathic Pharmacopoeia of the US (HPUS), which was recognized in the Food, Drug and Cosmetic Act with authority equivalent to the US Pharmacopoeia (USP).

The Homeopathic Pharmacopoeia is unique in several ways. First, there are over 2000 medications including plants, such as aconite and hellebore; minerals such as copper, gold and iodine; and animal products such as snake venom and tissue extracts. Second, medications are prepared as tinctures, (i.e. mixed with 95% grain alcohol), or as tiny pills with lactose fillers. Last, medications are dispensed in dilute solutions, from 1:10 to $1:10^1$

$^{000\,000}$, the latter dilution far beyond the point at which any molecules of the medicine can be expected still to be found in the solution. To date, no-one has been able to provide an adequate explanation for the possible mechanism of homeopathy.

Meta-analyses and reviews of research have come to different conclusions regarding the efficacy of homeopathy. While homeopathy is being used in the USA and the UK, there has been little research published in standard peer-reviewed journals regarding its clinical application. However, there is a vast homeopathic medical literature, some of which has been published continuously (and with consistent standards) since the 19th century. While 'classical' homeopathy is said by its proponents to be most effective in treating mental symptoms, the randomized, blinded trial literature is currently limited mainly to gastrointestinal and respiratory problems.

An example of the use of homeopathy in mental health is a study of 44 patients with generalilzed anxiety disorder[105]. Using a randomized, double-blind, placebo-controlled design, a 10-week trial of individually tailored homeopathic remedy was administered by an expert who followed the traditional routines of homeopathic diagnosis and prescription. Several measures were used including the Hamilton Rating Scale for Anxiety, the Brief Symptom Inventory, a Psychological General Well-Being Index, Spielberger's State-Trait Anxiety Inventory and a visual analog scale of subjective distress. While there was significant improvement on most measures in both the active treatment and placebo groups, no group effect was observed.

A review of 185 studies, 89 of which could be entered into a meta-analysis, concluded that 'the results of our meta-analysis are not compatible with the hypothesis that the clinical effects of homeopathy are completely due to placebo. However, we found insufficient evidence from these studies that homeopathy is clearly efficacious for any single clinical condition. Further research on homeopathy is warranted provided it is rigorous and systematic.'[106]

A comprehensive review of homeopathy for dementia is currently being conducted by the Cochrane Dementia and Cognitive Improvement Group[107].

It might be noted that the homeopathic evaluation process includes a holistic consideration of all physical and psychological characteristics of the patient and does not necessarily depend on a diagnosis. Like many forms of CAM, restriction to single therapeutic agents for particular diagnoses is believed to be an inappropriate way to evaluate the treatment.

## Massage

A check of one's local telephone directory will reveal a very large number of advertisements for a variety of massage therapies, among them deep tissue, sports, hot and cold stone, shiatsu, cranial sacral, seated chair, polarity, Swedish, reflexology, Esalen, Rolf, trigger point and prenatal. The various massage techniques include stroking, kneading, pinching, rubbing, knuckling, tapping or applying friction. Massage is most often performed with the hands and fingers, but vibrating machines and electrical stimulation are also used. Basically a treatment that involves manipulation of the soft tissues and the surfaces of the body, it reputedly was prescribed for the treatment of disease over 5000 years ago by Chinese physicians, and Hippocrates believed it to be an

important method of healing. Most people who experience massage find it physically and mentally relaxing and refreshing.

Massage may affect the body in several ways. It is said to increase blood circulation, improve the flow of lymph, sooth sore muscles and have a tranquilizing effect on the mind. Many mothers and pet-owners have remarked on the calming effects of massage on children or animals (and on themselves). A few preliminary studies have supported the perceived benefits of the treatment.

For example, 52 hospitalized depressed and adjustment-disordered children were treated with 30-min back massage given daily for a 5-day period. Compared to subjects viewing relaxing videotapes, massaged subjects were less depressed and anxious and had lower saliva cortisol levels after the massage. Nurses rated the subjects as being less anxious and more cooperative on the last day of the study[108].

One treatment effect that may contribute to the popularity of certain CAM practices is the salutary effect on the therapist… This appeared in a prayer study (reported below) and is an accepted belief in the bioenergetic treatment known as Reiki, in which a reciprocal exchange of energy is reputed to occur between the practitioner and the recipient of care. An interesting exploratory within-subjects comparison studied the effects of elderly retired volunteers giving massage to infants with receiving massage themselves[109]. Three times a week for 3 weeks, ten elder volunteers (eight women, mean age 70 years) received Swedish massage sessions. For another 3 weeks, three times per week, the same elderly volunteers massaged infants at a nursery school. Receiving massage first versus giving massage first was counterbalanced across subjects. After the sessions giving massages, the elderly retired volunteers had less anxiety and depression, and lower stress hormone (salivary cortisol) levels. Over the 3-week period depression and catecholamines (norepinephrine and epinephrine) decreased and lifestyle and health improved. These effects were not as strong for the 3-week period when they received massage.

Another study that examined the effects of administering massage suggested that learning the practice of infant massage by mothers is an effective treatment for facilitating mother-infant interaction in mothers with postnatal depression[110]. Thirty-four primiparous mothers were identified as being depressed by the Edinburgh Postnatal Depression Scale (EPDS) at 4 weeks' postpartum. Subjects were randomly allocated either to an infant massage class and a support group (massage group) or to a support group (control group). Each group attended for five weekly sessions. Changes in maternal depression and mother- infant interaction were assessed at the beginning and the end of the study by comparing EPDS scores and ratings of videotaped mother-infant interaction. While the EPDS scores fell in both groups, significant improvement of mother-infant interaction was seen only in the massage group. Although the sample size was small and had a relatively high drop-out rate, and it was not possible to distinguish which aspects of the infant massage class contributed to the benefit, the authors concluded that learning the practice of infant massage by mothers is an effective treatment for facilitating mother-infant interaction in mothers with postnatal depression. While these are clearly preliminary studies, they have examined the effects of a complementary health practice on the persons delivering the treatment.

### Peyotism or peyote religion: Native American Church

*Lophophora williamsi* (peyote) is obtained from the top of the peyote cactus. The substance contains mescaline, which is noted for its hallucinogenic and other mental effects. While substance abuse and self-exploration aspects of this preparation have been popularized, its most important use occurs in the Native American Church as part of a religious ritual which contains Native American and Christian components, and which promotes brotherly love, family care, self-support and avoidance of alcohol. The US Supreme Court has established a legal precedent that has significant implications for the religious use of peyote, and for sacramental use of all traditional drugs other than alcohol. It has been estimated that there are more than 225 000 members of the Native American Church. Peyote religion is a Native American pan-tribal religious system that employs the use of the peyote cactus—a practice depicted on tombs dating back to 100 BC.

Research on this topic is generally difficult, because of the multi-component nature of the 'treatment', the self-selection of the church members, lack of explicit standardization of the treatment and other factors such as the formation of social networks to help prevent relapse into alcoholism, and the participation by many in dance ceremonies held several times a year in various parts of the country. 'Treatment' may be a social system that has peyote as only one of its probable 'active' ingredients. The range of related practices includes sweat lodges, other herbs, cultural re-education and sun dances, among others. Research results have been contradictory, and recommendations that have been drawn from historical and epidemiological data have not been investigated by controlled research. Several factors probably contribute to outcome success in this area, as they do in all substance abuse research. Many health workers in the Indian Health Service of the US Public Health Service (USPHS) have seen long-term sobriety associated with Native American Church attendance by former inebriates. Physicians should note that participants and believers have a powerful conviction of its benefits. Many have experienced personal evidence for its salutary effects on not only substance abuse but also health, mental health and spiritual wholeness[111,112].

Regarding potential negative effects, three cases of botulism have been reported in members of the Native American Church who consumed peyote[113]. Thirteen church members ingested peyote from a communal jar during a ceremony. Two to four days' afterward, three men (40, 42 and 72 years old) noted the onset of bilaterally symmetric, moderate, flaccid weakness in all extremities. The ceremonial tea the patients had drunk was made from buttons of the dried, alkaline-ground peyote cactus, which had been covered with water and stored in a closed jar for 2 months under refrigeration. The author of the report believed that this prolonged, non-traditional storage of unsterilized peyote produced an anaerobic and alkaline environment that favored the growth and production of toxin from spores of *Clostridium botulinum* that were probably on the cactus. It was concluded that all ingested substances, including herbal medications and religious sacraments, must be considered as sources when botulism is suspected.

### Prayer: distant healing

In order to make the multiform practices of prayer amenable to research, operational definitions have been proposed. The act of prayer can be considered a form of 'distant healing', defined by Targ as: any purely mental effort undertaken by one person with the intention to improve the physical or emotional well-being of another (intercessory prayer)[114]. In a similar manner, the act of prayer can be self-administered and studied as part of the therapeutic process (personal or group prayer). An additional classification provided by Levin consists of a pair of dichotomous concepts which are based on whether healing has naturalistic or supernatural origins and whether it operates locally or non-locally[115]. Only a few research studies are listed here to indicate the variety of approaches and reported effects.

Experimental research has not addressed discrete psychiatric conditions in the manner used by pharmacological research. However, one large-sample, randomized, controlled, double-blind trial investigated the effects of directed and non-directed prayer and a control condition randomly assigned to 496 volunteers—those who prayed (agents, $n$=90) and those who were prayed for (subjects, $n$=406)[116]. Photographs and names of subjects were used as a focus. Agents were randomly assigned to either a directed or nondirected prayer group and patients were randomly assigned to the two forms of prayer or control group. Prayer was offered for 15min daily for 12 weeks. Each subject was prayed for by three agents. Five pretest and post-test objective measures and six post-test subjective measures were taken. On measures of self esteem, anxiety and depression the agents (those praying) showed significant improvement, better than the recipients of prayer (see above in the section on massage). Patient improvement was related to the subject's conviction concerning whether they had been assigned to a control or experimental group and to subjects' belief in the power of prayer for others. The author offered possible explanations including the placebo/faith effect and extraneous prayer. The research provides a good example of the special factors that need to be considered in this kind of research.

A survey research study indicated that 92% of a sample of inner-city homeless women reported one or more spiritual/religious practices[116], such as praying, attending worship services, or reading religious materials. Forty-eight per cent reported that prayer was significantly related to less use of alcohol and/or street drugs, and fewer perceived worries and depression.

There have been two major systematic reviews on this topic. The Cochrane Review of intercessory prayer for the alleviation of ill health concluded with the following:

> 'Data in this review are too inconclusive to guide those wishing to uphold or refute the effect of intercessory prayer on health-care outcomes. In the light of the best available data, there are no grounds to change current practices. There are few completed trials of the value of intercessory prayer, and the evidence presented so far is interesting enough to justify further study.
>
> If prayer is seen as a human endeavor it may or may not be beneficial, and further trials could uncover this. It could be the case that any effects

> are due to elements beyond present scientific understanding that will, in time, be understood. If any benefit derives from God's response to prayer it may be beyond any such trials to prove or disprove'[118].

Another recent systematic review of randomized trials of distant healing included prayer, mental healing, therapeutic touch, or spiritual healing as treatment for any medical condition[119]. Of the total of 23 trials involving 2774 patients who met the inclusion criteria, five examined prayer as the distant healing intervention, 11 assessed non-contact therapeutic touch, and seven examined other forms of distant healing. Of the 23 studies, 13 (57%) yielded statistically significant treatment effects, nine showed no effect over control interventions and one showed a negative effect.

The authors pointed out that in the UK today, there are more distant healers (about 14000) than there are therapists from any other branch of alternative medicine.

Of the five prayer studies, two trials showed a significant treatment effect on at least one outcome in patients being prayed for, and three showed no effect. Other interventions included 'distance or distant healing', 'paranormal healing', 'psychokinetic influence', and 'remote mental healing'. Four of seven trials indicated positive treatment effects. The authors concluded:

> 'Despite the methodologic limitations that we have noted, given that approximately 57% (13 of 23) of the randomized, placebocontrolled trials of distant healing that we reviewed showed a positive treatment effect, we concur with the summary conclusion of the Cochrane Collaboration's review of prayer studies that the evidence thus far warrants further study. We believe that additional studies of distant healing that address the methodologic issues outlined above are now called for to help resolve some of the discrepant findings in the literature and shed further light on the potential efficacy of these approaches.'

Some of the uneasiness that surrounds this topic is related to reports of the withholding of medical treatments with known efficacy because of a religious disbelief of the physical reality of the symptoms or illness or the 'spiritual dangers' of otherwise safe practices[120]. On the other hand, the salubrious social context of prayer—in the form of family and social community, shared reinforcement of beliefs and feelings, the comfort derived from social support and ideology at times of stress—all could be included in the total context within which a single ingredient, prayer, takes place.

The confounding effects of hope, expectation, relaxation, investigator bias and participation in other activities need to be taken into account in future research. In human substance abuse research, for instance, it remains to be determined whether prayer has efficacy in addition to its non-specific, personal treatment effects.

### Shamanism

This is an especially challenging form of CAM to evaluate for its effects on psychiatric conditions. The 'treatment' is a complex multi-component interactive process involving spiritual, cultural, social and technical aspects for the remedy of the total health, mental

health and spiritual condition of the person receiving treatment. It would seem less than optimal to select one condition and one aspect of the treatment in isolation from the total complex for the purposes of evaluating effectiveness. On the other hand, efforts in this direction have been made.

A shaman is an individual who is believed to have the power to heal the sick and to communicate with the spirit world, including primeval forces and spirits of the dead. The origin of the term appears to be from the Siberian and UralAltaic region, but individuals having this designation can be found in many parts of the world and, pertinent to this review, American aboriginal groups (first nations, Indians and Alaskan Natives). As a medicine man (or woman), qualifications are determined by a series of initiatory trials and the teaching and 'certification' by qualified, recognized Elders. These often include cleansing ceremonies (fasting, sweat lodge) and a 'vision quest'.

Through the experience of trance-like nies that deal with the individual's loss and states, the shaman conducts healing ceremorecovery of their soul. The ceremony is sometimes facilitated by rhythmic sounds, dancing, physical pain or privation and the use of 'spiritual herbs'. Through this process the shaman escorts the soul of the dying to the afterlife, or to spiritually determined solutions to insoluble personal or social problems[121,122].

Research on this topic is generally descriptive and philosophical. An example of a study employing preliminary research methodology is one study that examined the outcomes and satisfaction of 188 patients treated by shamans in Taipei, Taiwan with a matched sample of patients treated by physicians. Five 'distinctive sickness' (authors' terminology) types, including psychiatric problems, were involved. More than three-fourths of patients in both groups across the five sickness types perceived their health problems as improved and were similarly evaluated by the research staff. There was greater dissatisfaction with shamanistic treatment compared to the biomedical care. Patient attributions regarding the source of therapeutic efficacy were more complex and ambivalent compared to those of the research staff. The authors cited methodological limitations of the study and recommended that treatment outcomes should reflect not only biological factors but also cultural and socially constructed reality[123].

### Other religious beliefs and practices

In this chapter several of the above topics could be grouped under the terms of religious beliefs and practices, recognizing that only the most abbreviated treatment could be given to each topic. There remains the broadly defined application of the terms to existing research. For instance, a large body of epidemiological research indicates that religious beliefs and practices are negatively correlated with substance abuse and positively correlated with health status. Efficacy or causal explanations are primarily heuristic, however, and the investigation of these findings by clinical research methodology is just beginning.

There is one well-known and widely cited study that combined nearly all the desirable aspects of research design and measurement: a homogeneous baseline group including careful selection and exclusion criteria, use of accepted diagnostic and outcome measures, random assignment to treatments, waiting-list controls, post treatment and 3-month and 2-year follow-up, control for significant therapist variables, multivariate

analyses, monitored treatments, separate analysis of therapist religiousness and the religiously based cognitive behavioral therapy[124]. The clinically depressed patients were self-identified Christians. The religiously based cognitive therapy and the pastoral counseling patients obtained significantly improved post-treatment depression and adjustment scores compared to the non-religious cognitive therapy and the waiting-list controls. One interesting finding was the difference that was attributed to the superior performance of the non-religious therapists (with values dissimilar to those of the patient) in the religious therapy group. Improvement in all three groups was equal at follow-up and greater than the post-treatment waiting-list group effect. Generally, the findings indicated that religious subjects receiving religiously based cognitive behavioral therapy did better at post-treatment evaluation, regardless of the religiosity of the therapist conducting the therapy. Relevant to the discussion of this topic were the enduring effects of the pastoral counseling treatment that was used as one of the experimental controls.

Perhaps one secular observation of the above, pertaining to patient-doctor communication, would be the importance of finding the right wavelength for each patient, regardless of the personal prior beliefs of the therapist.

## NOCEBO EFFECTS

Placebo effects are fully discussed in another chapter in this text (see Chapter 12). Placebo effects in psychiatric treatment research have been referred to in several places in this chapter. However, it is important to call attention to one aspect of the placebo effect that can have significant psychiatric implications. The negative placebo outcomes that are associated with a medical or religious intervention are termed nocebo effects—results that worsen mental and/or physical health and intensify suffering. While the topic does not conform to the classifications as a CAM modality, psychiatric consequences and more generally described emotional distress can be evoked by the processes of both conventional and CAM treatments.

In a recent review of medication side-effects, several factors were associated with the reporting of non-specific side-effects: patient expectations of adverse effects; conditioning from prior experiences; certain psychological characteristics such as anxiety, depression and the tendency to somatize; and situational and contextual factors[125]. The review reported that approximately one-quarter of patients taking placebo reported adverse side-effects and, for diseases that are largely asymptomatic, the incidence of nocebo side-effects may equal or even exceed the incidence of side-effects reported by patients taking the active drug. A wide range of reactions included hypervagotonia manifested by an idioventricular rhythm, drowsiness, nausea, fatigue, insomnia, headache, weakness, dizziness, somnolence, gastrointestinal complaints and difficulty concentrating. The authors discussed methods of dealing with these symptoms in the context of research and clinical care.

A recent study by Mold and associates examined the effect of labeling on the perceived ability to recover from acute illnesses and injuries[126]. The authors reported that the process of giving a patient a diagnosis may cause harm. The adverse effects of labeling, best documented for the diagnosis of hypertension, included increased absenteeism from work and lower earnings, increased depressive symptoms and reduced

quality of life. In their study they found that the diagnosis of hypertension may affect patients' perceptions of their ability to recover from unrelated acute illnesses. This may have implications for the way physicians choose to present information to patients.

Even in apparently innocuous and apparently non-threatening treatments such as relaxation and biofeedback-assisted relaxation there are documented reactions of distress and disturbance. Schwartz and Schwartz list five classes of negative reactions that have been reported[127]:

(1) Musculoskeletal activity: cramps, tics, myoclonic jerks, spasms, restlessness.
(2) Disturbing sensory experiences: sensations of heaviness, warmth, cooling, depersonalization, misperceived body size, floating and a variety of visual, auditory, gustatory and olfactory experiences.
(3) Sympathetic nervous system activity: increased heart rate, increased electro-dermal activity.
(4) Cognitive-affective, emotional and intrusive thoughts: feelings of sadness, anger, depression, disturbing thoughts, intrusive thoughts or mind wandering, tearfulness, increased anxiety and fears such as fear of losing control.
(5) Other possible negative side-effects: hypotensive reactions, headache, sexual arousal and psychotic symptoms.

All of these reactions are discussed in detail with research evidence, rates of occurrence and recommendations on how to treat these incidents. References are provided.

There are a large number of case histories that describe intensification of illness or the production of death in various cultures, including reports in the USA. The topics of sudden death, hexes, curses, the consequences of taboo violations, voodoo death, and the production of aversive symptoms have been considered from various perspectives—anthropological descriptions, conditioned reflex learning, illusion of control studies, cerebral neurophysiology and sympathetic adrenal responses leading to cardiovascular collapse. Generally, these unintended negative consequences can be generated by medical and CAM practitioners who can be prepared to recognize and deal effectively with them.

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