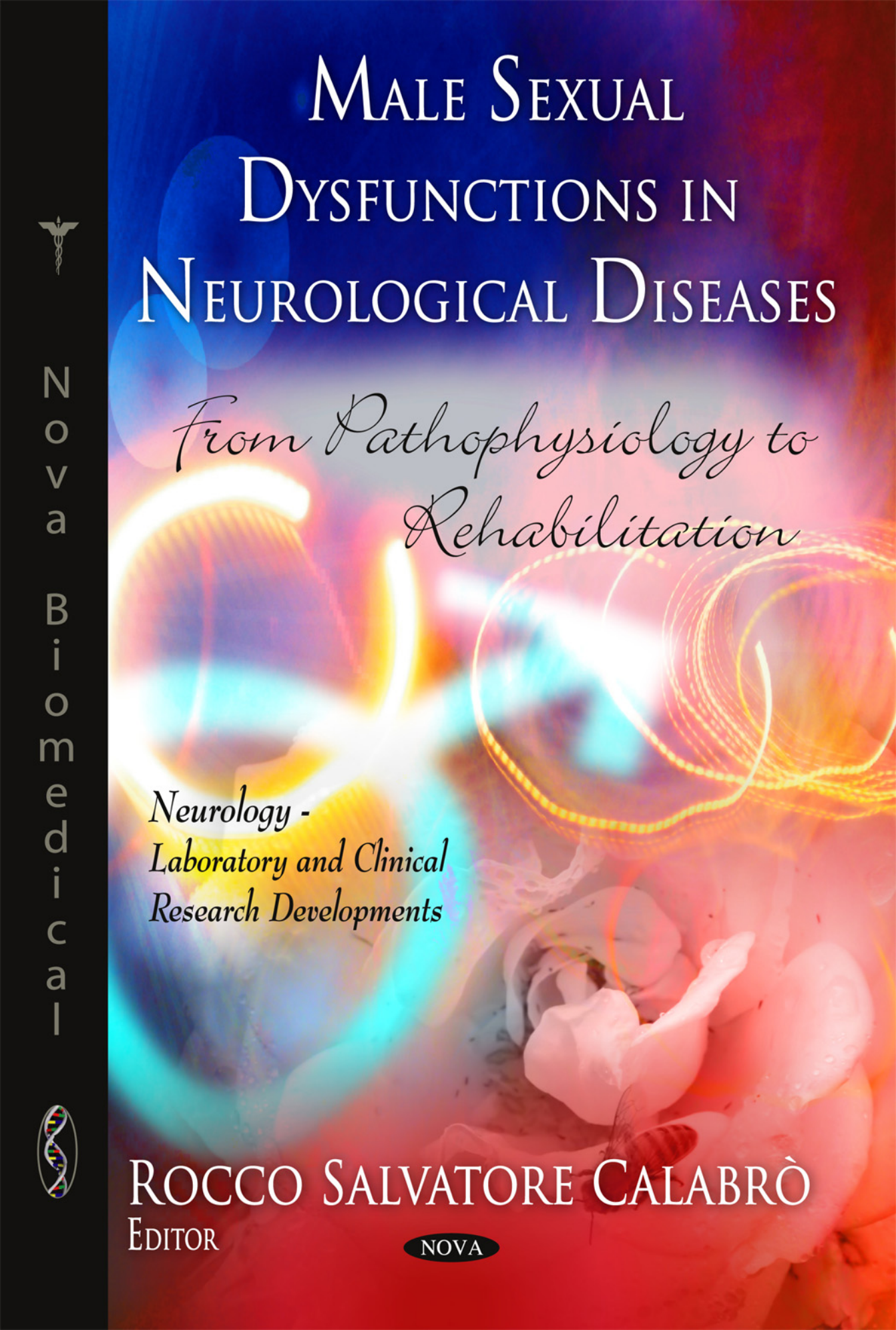

Male Sexual Dysfunctions in Neurological Diseases
From Pathophysiology to Rehabilitation
Neurology - Laboratory and Clinical Research Developments
Nova Biomedical
Rocco Salvatore Calabrò
Editor
NOVA

NEUROLOGY - LABORATORY AND CLINICAL RESEARCH DEVELOPMENTS

MALE SEXUAL DYSFUNCTIONS IN NEUROLOGICAL DISEASES: FROM PATHOPHYSIOLOGY TO REHABILITATION

NEUROLOGY – LABORATORY AND CLINICAL RESEARCH DEVELOPMENTS

Additional books in this series can be found on Nova's website under the Series tab.

Additional E-books in this series can be found on Nova's website under the E-book tab.

SEXOLOGY RESEARCH AND ISSUES

Additional books in this series can be found on Nova's website under the Series tab.

Additional E-books in this series can be found on Nova's website under the E-book tab.

NEUROLOGY - LABORATORY AND CLINICAL RESEARCH DEVELOPMENTS

MALE SEXUAL DYSFUNCTIONS IN NEUROLOGICAL DISEASES: FROM PATHOPHYSIOLOGY TO REHABILITATION

CALABRÒ ROCCO SALVATORE
EDITOR

Nova Science Publishers, Inc.
New York

Library of Congress Cataloging-in-Publication Data

Male sexual dysfunctions in neurological diseases : from pathophysiology to rehabilitation / editor, Rocco Salvatore Calabrr.
p. ; cm.
Includes bibliographical references and index.
ISBN 978-1-61122-189-3 (eBook)
1. Sexual disorders. 2. Impotence. 3. Men--Diseases. 4. Nervous system--Diseases--Complications. 5. Genitourinary manifestations of general diseases. I. Calabrr, Rocco Salvatore.
[DNLM: 1. Sexual Dysfunction, Physiological--physiopathology. 2. Men--psychology. 3. Nervous System Diseases--complications. 4. Sexual Dysfunction, Physiological--therapy. WJ 709]
RC877.M353 2010
616.6'922--dc22

2010034036

Published by Nova Science Publishers, Inc. † New York

Contents

To my son Mario

“There are only two tragedies in life: one is not getting what one wants, the other is getting it”. Oscar Wilde

Preface

All individuals, regardless of disability, are sexual beings.

Sexual function in patients with physical or neurological disabilities is often disregarded by healthcare professionals, though it is a topic of great importance to patients and to those with whom they share significant relationships. Too often, physicians believe that sexuality is not as important as the injury or illness that brought the patient to the rehabilitation team. The quality of personal relationships, sexual ones in particular, exerts great impact on a patient's self-esteem and support network. The multiple physical, psychological, and emotional changes that may occur after a catastrophic injury, or as a result of a congenital disability or chronic illness, must be addressed not only in the context of the patient, but also of the patient's support system. The issue of sexuality must be addressed during the acute and long-term rehabilitation processes. Sexual function recovery is no less important than any other aspect of functional rehabilitation from a disabling disease or injury. Indeed, people with disabilities are sexual individuals with sexual desires; their concerns require the attention of health care providers. The most popular myth surrounding people with disabilities is that they are less sexual than persons without disabilities. Entrenched socio-cultural beliefs have created significant barriers that prevent individuals with disabilities from exploring their sexuality; these false beliefs may be more disabling than physical impairment itself. The mention of a 'disabled' person engaging in sexual intercourse is guaranteed to raise a lot of eyebrows. An individual in a wheelchair is regarded as an object of pity, not of desire: being 'ugly' or overweight does not render a person asexual, but having a physical disability does. The worst part of this prejudice is that many people with disabilities believe this myth. People with a disability or a permanent illness may wonder whether they can have children, if their partners will stay with them, if anyone will find them sexually desirable, or if they will ever enjoy sex again. Many assume, incorrectly, that sexual intimacy is no longer possible due to sensation loss in the genitals since “sex means only sexual intercourse” and “sex is just genital pleasure and should necessarily end with orgasms”. Moreover, sex is often associated with youth and physical attractiveness and, when it is not, it is often seen as "unseemly". As a result, some may decide to ignore sexuality issues because they believe that they no longer apply to them; others will seek any opportunity to restore sexual-esteem. Questions, concerns, and feelings of anger regarding sexuality are natural in cases of disability or illness.

Neurological disorders frequently alter sexual response by changing the process of sexual stimuli to preclude arousal, decreasing or increasing desire, and curtailing genital engorgement. Patients with a neurological disease may challenge the physical ability to

communicate, embrace, stimulate, engage in intercourse, and maintain urinary and bowel continence during sexual activity. Thus, these patients, especially if male and young, may regard their sexual loss to be its most devastating aspect. Subjects, in particular those affected by neurological disorders, should be questioned about their sexuality in order to address possible sexual dysfunction. Epilepsy, demyelinating disorders, brain and spinal cord injuries, and the treatment used in these diseases, may often cause erectile and/ or ejaculation dysfunctions; it may also affect sexual desire in young men. Furthermore, alterations in the sexual area of patients with cerebrovascular diseases and neurodegenerative disorders may exacerbate their quality of life. When sex and disability are discussed while counseling a neurological patient, it is solely in terms of capacity, technique, and fertility - in particular, male capacity and technique and female fertility—with no reference to sexual feelings. This approach ignores other aspects of sexuality, such as touching, affection, and emotions. Prior to the 1970s, minimal research was conducted regarding sexuality and disability. The topic was traditionally considered personal, private and not a necessary component of one's rehabilitation and overall health. Fortunately, over the past 20years, research on sexuality and disability is growing, since sexual well being is nowadays considered one of the most important aspects of one's quality of life.

This book aims to investigate sexual function in persons with neurological disorders, highlighting the importance of proper counseling, diagnosis and treatment. The book may be an important guide for specialists who are involved in the neurological aspects of human sexuality; also it may form the basis for a better assessment and management of sexual dysfunction in neurological diseases. Indeed, the issues treated range from the anatomophysiology of human sexuality to the treatment and rehabilitation of sexual disorders; taking into account the psychological aspects of sexual function and the role of major neuropsychiatric diseases in the pathogenesis of sexual dysfunction.

Acknowledgment

The editor would like to thank Professor **Agata Grosso** for revising the manuscript in the English language.

In: Male Sexual Dysfunctions in Neurological Diseases… ISBN 978-1-61761-855-0
Editor: Calabrò Rocco Salvatore

Chapter 1

Neuroanatomy and Physiology of Human Sexuality

Rocco Salvatore Calabrò and Placido Bramanti
IRCCS Centro Neurolesi "Bonino-Pulejo", Messina

Abstract

Sexual desire, arousal, and orgasm are mediated by complex, but still yet not fully understood, interactions of the somatic and autonomic nervous systems, operating at cerebral, spinal and peripheral levels. At the central level, dopaminergic and serotonergic systems appear to play a significant role in various components of sexual response, although adrenergic, cholinergic, nitrergic, γ-aminobutyric acidergic, and other neuropeptide transmitter systems may contribute as well. Furthermore, neural activity within these systems is modulated by the presence of steroid and peptide hormones, which affect male and female response differentially. At the peripheral level, adrenergic, cholinergic, and nitrergic activation mechanisms control vascular changes that underlie vaginal lubrication and penile erection. In addition, these systems respond to descending brain and spinal influences that generate pleasure and orgasmic response. Disruption of endocrine, neural, or vascular response, caused by aging, medical illness, neurological diseases, surgery, or drugs has the potential to lead to sexual dysfunctions.

Human Sexual Cycle

The human sexual response cycle is a four-stage model of physiological responses during sexual stimulation, proposed for the first time by William H. Masters and Virginia E. Johnson in their book *Human Sexual Response* (1966) and composed of the sequential phases of excitement, plateau, orgasm, and resolution [1]. Later, Kaplan proposed a new model of sexual response, incorporating the three components of desire, excitement, and orgasm, showing the interdependence among the response phases: problems with orgasm could result from insufficient arousal; or problems with arousal might occur in the desire phase [2]. This

triphasic model has had strong appeal because its components coincide with problems typically encountered by clinicians: lack of interest in sex, inability to become aroused (i.e., get an erection), or difficulty with orgasm (i.e., premature ejaculation, delayed orgasm, or anorgasmia).

1) Desire Phase

Sexual desire is commonly defined as the broad interest in sexual objects or experiences. As desire is not objectively evaluated, it is generally inferred by self-reported frequency of sexual thoughts, dreams, fantasies, wishes and interest in initiating and engaging in sexual experience. Desire is influenced by many factors such as attitudes, opportunity and/or partner availability, mood and health.

2) Excitement Phase

The excitement phase is the second stage of the human sexual response cycle. It occurs as the result of any erotic physical or mental stimulation, such as kissing, petting, or viewing erotic images that lead to sexual arousal. Intimately connected with sexual desire, sexual arousal is defined in both subjective (i.e. feeling sexually excited) and physiological terms (i.e., genital vasocongestion). During the excitement stage, the body prepares for coitus or sexual intercourse. In males, physiological sexual arousal firstly involves the regulation of penile hemodynamic that depends on signal input from central and peripheral nervous systems, and on a complex interplay between neurotransmitters, vasoactive agents and endocrine factors. The erection may be partially lost and regained repeatedly during an extended excitement phase. Both testicles become drawn upward toward the perineum, notably in circumcised males where less skin is available to accommodate the erection. Besides the scrotum can tense and thicken during the erection process.

Furthermore, the excitement phase results in an increase in heart rate, an increase in breathing rate, and a rise in blood pressure. An erection of the nipples, especially upon direct stimulation, will occur in approximately 60% of males. Vasocongestion of the skin, commonly referred to as sex, will occur in approximately 25-30% of males. During the male sex flush, the coloration of the skin develops less consistently than in the female one, but typically starts in the epigastrium (upper abdomen), spreads across the chest, and then continues to the neck, face, forehead, back, and sometimes, shoulders and forearms. The sex flush typically disappears soon after orgasm occurs, but this may take up to two hours, and sometimes, intense sweating will occur simultaneously.

3) Orgasmic Phase

Orgasm is the conclusion of the plateau phase of the sexual response cycle. It is accompanied by quick cycles of muscle contraction in the lower pelvic muscles, which surround both the anus and the primary sexual organs. Orgasm is often associated with other involuntary actions, including vocalizations and muscular spasms in other areas of the body,

and a generally euphoric sensation. The heart rate increases even further. In men, orgasm is usually associated with ejaculation. Each spurt is associated with a wave of sexual pleasure, especially in the penis and loins. Other sensations may be felt strongly among the lower spine, or lower back. The first and second convulsions are usually the most intense in sensation, and produce the greatest quantity of semen. Thereafter, each contraction is associated with a diminishing volume of semen and a milder wave of pleasure.

The *resolution phase***,** not considered in Kaplan cycle**,** occurs after orgasm and allows the muscles to relax, blood pressure to drop and the body to slow down from its excited state. Men usually experience a refractory period, that varies from human to human, with some being immediate (no refractory) and some being as long as 12 to 24 hours. Sometimes further stimulation may cause a return to the plateau stage that allows the possibility of multiple orgasms (more commonly in females); but more often men typically enter this refractory period and may find continued stimulation to be painful after the orgasmic phase [3].

Neuroanatomy of Human Sexual Behavior

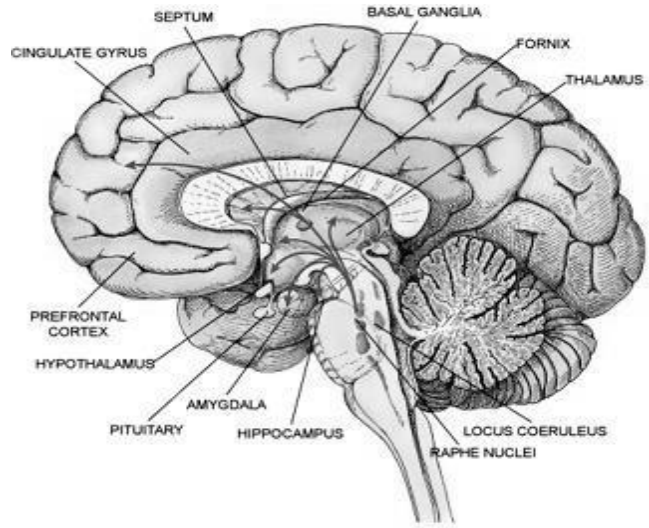
All behaviors have a beginning, a middle and an end, and all organisms that engage in sexual behavior share a common set of principles and end points that define the behavior, along with particular neural mechanisms that make it successful. Neural pathways that allow sexual responding to become habitual or automated with practice and those associated with positive sexual reinforcement (reward) have been demonstrated in animals and are thought to be present in humans too [4]. In neuroscience, the *reward system* is a collection of brain structures which attempts to regulate and control behavior by inducing pleasurable effects. A psychological reward is a process that reinforces behavior, something that, when offered, causes a behavior to increase in intensity. Reward is an operational concept for describing the positive value an individual ascribes to an object, behavioral act or an internal physical state. Natural rewards include those that are necessary for the survival of species, such as eating, drinking, sex, and fighting. Secondary rewards derive their value from the primary reward, and include shelter, money, pleasant touch, beauty, music, etc. The functions of rewards are based directly on the modification of behavior and indirectly on the sensory properties of rewards. Rewards are generally considered more effective than punishment in enforcing positive behavior. Rewards induce learning, approach behavior and feelings of positive emotions. The major neurochemical pathway of the reward system in the brain involves the mesolimbic and mesocortical pathway. Of these pathways, the mesolimbic pathway probably plays the major role, and goes from the ventral tegmental area via the medial forebrain bundle to nucleus accumbens, where dopamine is primarily released.

The key brain regions mediating human sexual behavior, shown in figures 1a and 1b, have been identified in human literature examining the effect of neurological insult on sexual behavior and through recent functional neuroimaging findings [5]:

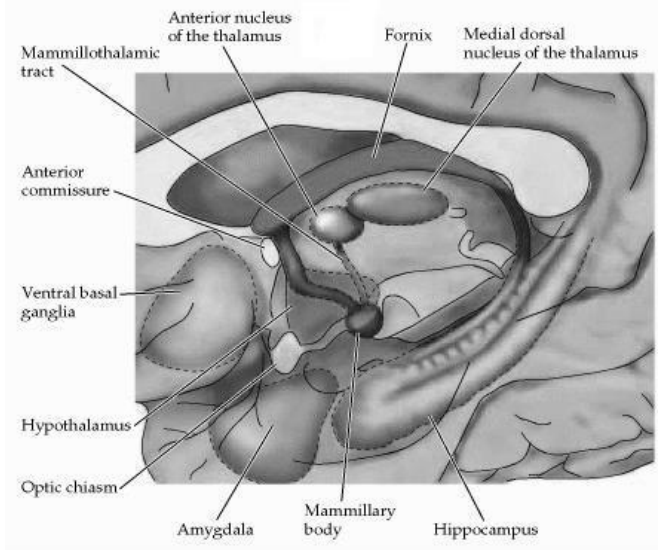
1) the *hypothalamus* that mediates neuroendocrine and autonomic aspects of sexual drive and is thought to be responsible for sexual orientation;
2) the *septal region*, involved in the mediation of orgasm and sexual pleasure;
3) the *ansa lenticularis* and *pallidus* implicated in sexual drive;

4) the *frontal lobes*, in particular the prefrontal cortex, involved in the motor components of sexual behavior and the control of sexual response ;
5) the *parietal lobes*, in particular the paracentral lobule, implicated in genital sensation;
6) the *temporal lobes*, with particular regard to the *amygdala*, involved in sexual orientation, sexual drive and sexual dysfunctions (i.e. paraphilia) and to the *hippocampus*, responsible for both emotion and memory in relation to the complex cerebral modulation of sexual behavior.

1a



1b



Figures 1a and 1b show the main brain regions involved in sexual behavior with particular regard to the limbic system.

Other important areas such as nucleus paragigantocellularis (nPG1), locus ceruleus (LC), rafhe nuclei, periaqueductal gray area are located in the brainstem and intimately connected to the spinal cord and are mainly involved in erection and ejaculation. Moreover insula seems to play an important role in sexual behavior modulating homeostasis and emotions [5].

Hypothalamus

The hypothalamus is a portion of the brain that contains a number of small nuclei with a variety of functions. One of the most important functions of the hypothalamus is to link the nervous system to the endocrine system via pituitary gland. The hypothalamus is located below the thalamus, just above the brain stem. In the terminology of neuroanatomy, it forms the ventral part of the diencephalon. Hypothalamus is responsible for certain metabolic processes and other activities of the autonomic nervous system. It synthesizes and secretes neurohormones often called hypothalamic-releasing hormones, and these in turn stimulate or inhibit the secretion of pituitary hormones. The hypothalamus controls body temperature, hunger, thirst, circadian cycles and sexual drive. It has been demonstrated that focal lesions of the hypothalamus result in a reduction or abolition of sexual drive while lesions including but not restricted to this structure result in increased sexual drive. This paradox may reflect the complexity of the hypothalamus, the key brain region mediating neuroendocrine and autonomic aspects of human sexual drive, and its associations with many other brain regions and the possibility that different hypothalamic nuclei serve opposing functions. The medial preoptic and anterior area (MPOA) modulates erection and coordinates autonomic events associated with sexual response. The paraventricular nucleus (PVN), producing oxytocin, is activated during copulation and orgasm. The anterior hypothalamus of the brain participates in the regulation of male-typical sexual behavior; in particular, INAH3 is dimorphic with sexual orientation, at least in men, and suggests that sexual orientation has a biological substrate as it is smaller in women and gay-men [6-7-8-9].

Amygdala

The amygdala is almond-shaped groups of nuclei located deep within the medial temporal lobes of the brain in complex vertebrates, including humans. Amygdala plays a primary role in the processing and memory of emotional reactions so to be considered part of the limbic system. The region described as amygdala encompasses several nuclei with distinct functional traits: the basolateral complex, the centromedial nucleus (that may be considered as a part of the basal ganglia) and the cortical nucleus. The amygdala sends impulses to the hypothalamus for important activation of the sympathetic nervous system; to the thalamic reticular nucleus for increased reflexes; to the nuclei of the trigeminal nerve and facial nerve which implements facial muscle movements; and to the ventral tegmental area (VTA), LC, and laterodorsal tegmental nucleus for activation of dopamine, norepinephrine and epinephrine. The cortical nucleus is involved in the sense of smell and pheromone-processing as it receives input from the olfactory bulb and olfactory cortex. The lateral amygdala, which sends impulses to the rest of the basolateral complexes and to the centromedial nuclei, receives input from the sensory systems. The centromedial nuclei are the main outputs for the

basolateral complexes, and are involved in emotional arousal in animals and humans. All these complex neuronal interconnections underline the amygdala pivotal role in human sexual drive [10-11-12]

Prefrontal Cortex

The prefrontal cortex (PFC) is the anterior part of the frontal lobes of the brain, lying in front of the motor and premotor areas. This brain region has been implicated in planning complex cognitive behaviors, personality expression, decision making and moderating correct social behavior. The basic activity of this brain region is considered to be the orchestration of thoughts and actions in accordance with internal goals. The most typical psychological term for functions carried out by the pre-frontal cortex area is executive function. Executive function relates to the abilities to differentiate among conflicting thoughts, determine good and bad, better and best, same and different, future consequences of current activities, working toward a defined goal, prediction of outcomes, expectation based on actions, and social "control" (the ability to suppress urges that, if not suppressed, could lead to socially-unacceptable outcomes).

It is assumed that sexual inhibition is an adaptive response that serves both reproductive and social end points, for example, to keep individuals out of trouble or to allow a sufficient amount of sexual satiety that appears as a “refractory phase”. Inhibition is related to the executive functions, viewed as the role of the PFC, which must inhibit a complex and ongoing interplay of motor tendencies to planned and sustained actions. With regard to sexual behavior it is assumed that cultures superimpose a moral value of “right” and “wrong” on the hierarchies so that some behaviors that feel good are right and can be experienced without guilt, whereas others are wrong and carry the weight of guilt and/or rule of law against them. Thus, this type of inhibition represents an approach-avoidance conflict, where the expectation of reward drives the desire, but the real or perceived aversive consequences of engaging in sexual activity blunts the initiation of behavior. Moreover sexual inhibition can also be induced by sexual non-reward suppressing directly desire components. Accordingly, the “prosexual” nature of drugs such as alcohol or cocaine may act through the ability to disinhibit such suppressed sexual responding. This inhibitory systems are located in the PFC and exist to inhibit the activation of excitatory mechanisms and possibly to shift attention and behavior to nonsexual stimuli or situations. Opioids, which mediate sexual reward states, endocannabinoids, which induce sedation, and serotonin, which induce satiety seem to be, at least, the three neurochemical systems involved in sexual inhibition [13].

Sexual Desire and Sexual Arousal

As better specified before, sexual desire or libido is defined as the broad interest in sexual objects or experiences, while sexual arousal is both a subjective (i.e. feeling sexually exited) and a physiological (i.e. genital vasocongestion) terms. While sexual hormones have a critical role in modulating sexual arousal, sexual desire seems to be initiated by the reception/ perception of sexual *pheromones.*

Pheromones are substances secreted by glands in the anus, urinary outlet, breasts, and mouth. In nonhuman mammals, a specialized olfactory structure, the vomeronasal organ, acts as the anatomic locus for pheromonal signals. The vomeronasal organ has been identified in humans, but, to date, there have been no human studies linking behavioral change and stimulation of vomeronasal organ receptors. Generally, it is known that male pheromones (androstenol and androstenone from male sweat) have a direct impact on female sexual desire, menstrual cycles and ovulation. Likewise, female vaginal pheromone (copilins) influences the male perception of the female and might induce hormonal changes. It is clear now that sexual attraction between the human genders and, in part, sexual orientation is modulated by sexual pheromones [14-15].

The mechanisms underlying generalized arousal are complex and involve many cerebral circuits [16]. Regarding ascending pathways, five major neurochemical systems are classically recognized as contributing to the arousal of the forebrain, i.e. those signaled by norepinephrine, dopamine, serotonin, acetylcholine and histamine, while the role of glutamate is less widely recognized. Of special importance to the regulation of CNS arousal are the reticular neurons along the ventral and medial borders of the medullary and pontine reticular formation, that are crucial to the life of the organism as they respond to pain, genital sensation, to CO2 levels in the blood, to changes in body temperature and cardiovascular functions. Other important axons descend from the paraventricular nucleus and from the preoptic area of the hypothalamus affecting all the arousal aspects. A neurobehavioral and multifaceted model of neural mechanisms for sexual arousal has been proposed which includes a cognitive, an emotional, a motivational, and an autonomic component.

Cerebral areas which have been found to be linked to the cognitive mechanism include the ‘‘attentive’’ network relaying in orbitofrontal cortex and the superior parietal lobules, motor imagery in inferior parietal lobules, while the motivational component would be stored in the caudal part of the anterior cingulate cortex, related to motor preparation processes; finally, the autonomic mechanism would involve the hypothalamus, insula, and the rostral part of the anterior cingulate cortex.

In particular neural pathways of sexual arousal due to visual stimuli have been recently identified [17]. This circuit includes limbic (hypothalamus, hippocampus and amygdala) and paralimbic areas (anterior cingulate gyrus, frontal lobe, and insula), associative cortices (inferior temporal and occipital cortices), and other subcortical and cortical sensory relays (thalamus and secondary somatosensory cortex or SII). It can be hypothesized that the autonomic and endocrine control of sexual behavior is mediated by the hypothalamus, while the activation of the amygdala is related to the appraisal process through which erotic stimuli are evaluated as sexual incentives. Indeed, the amygdaloid complex receives multimodal sensory input, as well as input from the hippocampal formation, the thalamus, and the association cortices, and relays processed information to the ventral striatum, hypothalamus, autonomic brainstem areas, and the prefrontal cortex. These findings support the neurobehavioral model that the amygdala participates in the evaluation of emotional content of the complex perceptual information associated with the visual processing of the erotic stimuli. The insula seems to be linked to the activation to the somatosensory processing pathway: the activation in this area, together with thalamic and SII activation, may therefore reflect the participant’s perception of his own behavioral response. Finally, the anterior cingulate gyrus and the prefrontal cortex play a role in the evaluation of the motivational/emotional information and in the initiation of goal-directed behavior, since these

areas are specifically related to the monitoring and the control of emotionally driven behaviors. Even if less studied in humans, olfactory stimuli play an important, but often unconscious, role in sexual arousal: the specific anatomical pathway involves the rhinencephalon including cingulated gyrus, septum and hippocampus.

Neurobiology of Sexual Function

Within the past decade, increasing research attention has been paid to the neurobiology of sexual function. This has been fostered by growing awareness of the deleterious effects of pharmacological agents on sexual behavior, by an increased recognition of the high incidence of difficulties in men, by the enormous success of using the phosphodiesterase inhibitors for the treatment of erectile dysfunction. In this paragraph we provide a brief report of the role played by the most important endocrine and neurotransmitter factors in male sexual function.

Serotonin

Serotonin is a monoamine neurotransmitter, found extensively in the gastrointestinal tract of animals, as about 80 to 90% of the total serotonin in the human body is located in the enterochromaffin cells of the gut, where it is used to regulate intestinal movements. The remainder is synthesized in serotonergic neurons in the central nervous system (CNS), where it has various functions, including the regulation of mood, appetite, sleep, muscle contraction, and some cognitive functions including memory and learning. Serotonin has broad activities in the brain, and genetic variations in serotonin receptors and in the serotonin transporter, which facilitates re-uptake of serotonin into presynapses, have been implicated in neurological diseases. The neurons of the raphe nuclei are the principal source of 5-HT release in the brain. The raphe nuclei are neurons grouped into about nine pairs and distributed along the entire length of the brainstem, centered on the reticular formation. Axons from the neurons of the raphe nuclei form a neurotransmitter system, reaching large areas of the brain. Axons of neurons in the *caudal* raphe nuclei terminate in deep cerebellar nuclei, cerebellar cortex and spinal cord. Axons of neurons in *rostral* raphe nuclei terminate in the thalamus, striatum, hypothalamus, nucleus accumbens, neocortex, cingulate gyrus, cingulum, hippocampus, amygdalae. Thus, activation of this serotonin system has effects on large areas of the brain and seems to be involved in sexual behavior.

Approximately 95% of serotonin receptors are located in the periphery of the body where serotonin acts on the smooth muscles of the vascular system of the genitals and other sexual organs to produce vasoconstriction and vasodilatation.

In CNS, 5-HT has an inhibitory effect on male sexual function. Antidepressants of the selective serotonin reuptake inhibitor class (SSRI) impair ejaculatory/orgasmic function and frequently inhibit erectile function and sexual interest as well. Interestingly, experimental lesions of a major source of 5-HT to spinal cord, i.e. nPG1, disinhibit the urethrogenital reflex (a model of sexual climax) and reflexive erections and penile anteroflexions, confirming the potential inhibitory role of serotonin on sexuality.

5-HT receptors are highly heterogeneous and they have been regrouped within seven different families. Whereas all the 5-HT receptor subtypes are found postsynaptically and appear to mediate an inhibitory effect on ejaculation and erection, only 5-HT1A and 1B/D receptors are located pre-synaptically where they mediate the negative feedback of serotonin on its synaptic release. Stimulation of 5-HT1A receptors, either systematically or in the MPOA, facilitated ejaculation, and systematic administration of a 5-HT1A agonist reversed sexual satiety. Thus, it was suggested that 5-HT1A agonists' beneficial effects may result from their stimulation of the inhibitory autoreceptors in the raphe nuclei, which would decrease 5-HT levels. Otherwise, the facilitative effects of the 5-HT1A agonist may be mediated in part through its increase in extracellular dopamine in the MPOA. Moreover, as 5HT1a receptors are found in the dorsal horn and dorsal gray matter commissure, it is likely that these receptors are involved in the spinal processing of sensory information to the brain also modulating the triggering of ejaculation [18-19].

Dopamine

Dopamine is a neurotransmitter, acting in the brain through the activation of five types of dopamine receptors - D_1, D_2, D_3, D_4, and D_5, and their variants. Dopamine is produced in several areas of the brain, including the substantia nigra and the VTA and is also released by the hypothalamus to inhibit the release of prolactin from the anterior lobe of the pituitary.

The four major dopaminergic pathways are:

- the *mesocortical* pathway transmitting dopamine from VTA to medial PFC, a region implicated in executive control and inhibition; malfunctions of this pathway are associated with schizophrenia.
- the *nigrostriatal* pathway, from the substantia nigra to the striatum (i.e. caudate and putamen nuclei); this pathway is associated with motor control, and its degeneration is related to Parkinson's disease.
- the *tuberoinfundibular* pathway that transmits dopamine from the hypothalamus to the pituitary gland, influencing the secretion of certain hormones, including prolactin.
- the *mesolimbic* pathway projecting diffusely from the VTA to different limbic and cortical structures, including several amygdale nuclei, nucleus accumbens (NAc), olfactory tubercle and piriform cortex, lateral septum and anterior cingulated cortex, which plays a pivotal role on sexual behavior and reward.

The role of dopamine in human sexuality is not completely understood yet and most of our knowledge comes from animal models (Hull 2004). Dopamine in the striatum disinhibits pathways through which the cortex elicits movements: this neurotransmitter is released during copulation, but not during precopulatory exposure to a receptive female, suggesting that striatal dopamine is important for motor aspect of copulation, but not for sexual motivation. Indeed, the mesolimbic system is critical for appetitive behavior and reinforcement; in fact, it is activated before and during a variety of motivated behaviors, including eating, drinking, copulating and drug-self administration. Furthermore, dopamine in the MPOA facilitates male

sexual behavior in many species, suggesting that it plays a central role in this process. MPOA receives indirect sensory input from every sensory modality but the dopamine input arises from periventricular system. Efferent projections are to hypothalamic, midbrain and brain stem nuclei positively regulating sexual autonomic or somatomotor patterns and motivational states.

The pivotal role of dopamine in human sexuality is partially confirmed by the fact that dopaminergic drugs have long been known to facilitate masculine sexual function clinically. In fact, it has been demonstrated that the classic dopamine agonist apomorphine is effective in treating erectile dysfunction with fewer side effects.

Interestingly, cocaine enhances dopamine activity by blocking the presynaptic autoreceptors so that cocaine is commonly believed to enhance sexual pleasure. Low doses of cocaine may enhance sexual enjoyment by stimulating the limbic system and by delaying ejaculation, but, on the other hand, studies on cocaine addicts suggest that the drug chronic use may impair sexual functioning.

Dopaminergic pathways are regulated by both neurosteroids, in particular testosterone, and many other neurotransmitters such as serotonin, noradrenaline, glutamate, and nitric oxide.

In conclusion, dopamine, released in several major areas before and/or during copulation, facilitates sexual motivation, motor performance, and genital reflexes. Small increases in dopamine in MPOA disinhibit genital reflexes via a member of D2 receptors; moderate increases facilitate parasympathetically mediated erections and copulatory behavior via D1-like receptor; large increases promote sympathetically mediated ejaculation but inhibit erections [19-20-21].

Noradrenaline and Adrenaline

Noradrenaline or norepinephrine (NE) is a catecholamine with dual roles as a hormone and a neurotransmitter. NE is synthesized from dopamine by dopamine β-hydroxylase. As a stress hormone, NE is released from the adrenal medulla into the blood and affects the body and parts of the brain where attention and responding actions are controlled. In fact, along with epinephrine, NE underlies the fight-or-flight response, directly increasing heart rate, triggering the release of glucose from energy stores, and increasing blood flow to skeletal muscle.

When NE acts in the autonomic nervous system, it increases blood pressure by its prominent effects on the vascular tone from α-adrenergic receptor activation. The resulting increase in vascular resistance triggers a compensatory reflex that overcomes its direct stimulatory effects on the heart, called the baroreceptor reflex, which results in a drop in heart rate called reflex bradycardia.

The noradrenergic neurons in the brain form a neurotransmitter system, that, when activated, exerts effects on large areas of the brain. The effects are alertness and arousal, and influences on the reward system. Anatomically, the noradrenergic neurons originate both in the locus coeruleus and the lateral tegmental field. The axons of the neurons in the locus coeruleus act on adrenergic receptors in: amygdala, cingulate gyrus, cingulum, hippocampus, hypothalamus, neocortex, spinal cord, striatum, and thalamus. On the other hand, axons of neurons of the lateral tegmental field act on adrenergic receptors in the hypothalamus.

So, NE release in different regions of the brain controls different aspects of motivation with an "inverted U-shaped curve" in which an optimal of NE transmission supports an optimal level of behavior but in which a high amount of transmission disrupts behavior by producing generalized fear response. NE binds to two classes of receptor, classically termed "α" and "β" respectively, and differentiated according to whether the receptor stimulates (β) or inhibits (α) the activation of the second messenger adenylate cyclase. The α-receptors are further classified into α1 and α2 subtypes, which are found postsynaptically or postsynaptically, respectively. Adrenergic activity plays a role in maintaining the penis in a flaccid state and in producing detumescence. A_1-adrenergic receptors have been found in human penile tissue and blockade of α1-receptors produces an erection.

Studies reporting the effects of drugs that act on NE receptors indicate that NE is important in sexual function in men. As noted earlier SSRIs produce a whole host of side effects while the newer classes of antidepressant that act on NE neurotransmission (i.e. venlafaxine, duloxetine, mirtazapine) have been found to produce fewer side effects.

Interestingly, administration of the α2 antagonist yohimbine stimulates penile erection via autonomic activation and can reverse the sexual inhibition that follows sexual exhaustion in male rats; moreover it is known that this drug is useful in the treatment of erectile dysfunction and anorgasmia [18, 22].

Acetylcholine

The chemical compound *acetylcholine (Ach)* is a neurotransmitter in both the peripheral nervous system (PNS) and central nervous system (CNS) in many organisms including humans. Ach activates muscle contractility through the binding to Ach-receptors on skeletal muscle fibers opening ligand gated sodium channels in the cell membrane with a consequent increase in intracellular calcium. As the major neurotransmitter of the autonomic nervous system, Ach is released in the following sites:

- all pre- and post-ganglionic parasympathetic neurons
- all preganglionic sympathetic neurons (preganglionic sympathetic fibers to suprarenal medulla, the modified sympathetic ganglion; on stimulation by acetylcholine, the suprarenal medulla releases epinephrine and norepinephrine)
- some postganglionic sympathetic fibers (sudomotor neurons to sweat glands).

Ach, together with vasoactive intestinal peptide, has been implicated in penile erection. Erection occurs when the smooth muscles of the corpus cavernosum relax permitting increased blood flow into the penile tissue. The human corpus cavernosum is innervated by cholinergic nerves and contains cholinergic receptors suggesting endogenous activity of the Ach in the penile tissue. The cholinergic agent bethanecol has been reported to be useful in reversing antidepressant-induced erectile and ejaculation difficulties [18, 22].

Hystamine

Histamine functions detected as neurotransmitter-like or neuromodulator-like have been identified in many brain areas. A typical action of histamine is that it excites neurons by producing a depolarization and a subsequent increase in firing frequency. Histamine actions have been studied in the ventromedial nucleus of the hypothalamus (VHM) and its potential in modulating VMH functions, such as sexual behavior and feeding behavior, is well established.

The H2 antagonists, cimetidine and ranitidine, have been shown to cause loss of libido and erectile failure and it may partially result from reduction in uptake of testosterone.

Peripherally, histamine is implicated in penile vasodilatation as its injection into the corpus cavernosum produces full or partial erection through the activation of H2 and H3 receptors [23].

Opioids

Much of what is known about the role of opiods in the sexual response cycle comes from research on the effect of narcotics and agonists and antagonists of naturally occurring opiods such as endorphins, enkephalins and dynorphins. Indeed, it is well established that abuse of opiods leads to loss of libido, erectile dysfunction, inability to reach orgasm. Withdrawal from opiate addiction is characterized by increased frequency of morning erections, spontaneous ejaculation and a slow return to sexual drive. Although the mechanism by which opiates affect sexual functioning is unclear, evidence suggests that the increasing in opiod activity produces a decrease in the levels of circulating hormones, such as LH and testosterone with consequent sexual impairment.

Sex Hormones

Sex steroids, or gonadal steroids, are steroid hormones that interact with androgen or estrogen receptors. Their effects are mediated by slow genomic mechanisms through nuclear receptors as well as by fast non-genomic mechanisms through membrane-associated receptors and signaling cascades

Sex hormones are essential for neural circuit development and sex-specific-behaviors. Male behaviors require both testosterone and estrogen, but it is still unclear how the two hormonal pathways intersect. Circulating testosterone activates the androgen receptors (ARs) and is also converted into estrogen in the brain via aromatase; it seems that this conversion, especially in the critical periods of the brain development, is important for sexual behavior, differentiation and orientation.

In most species sexual behavior principally serves the purpose of reproduction. Biological differentiation into male and female makes sexual reproduction possible. Males have two sex chromosomes (X and Y); females are XX. Sexual differentiation is determined by the presence or absence of the Y chromosome so that if Y is absent, development is along female lines. In particular, the SRY (sex-determining gene region of the Y chromosome) is responsible for male differentiation, i.e. for the development of the primitive gonad into testis,

where Leydig cells produce testosterone. The testosterone stimulates development of male genitalia and reproductive organs and moreover, has organizing effects on the CNS. Within the brain testosterone binds to ARs, but can be converted in Dihydrotestosterone (DHT) through the 5-alpha reductase pathway and bind to AR, or to estradiol through the aromatase pathway and bind to estrogen receptors (ERs) which act to masculinise (increase male-typical behaviours) and definiminise (reduce male typical responses) the behavioural development of male mammals. ARs are widely found in cerebral and subcortical regions of the human brain (MPOA, SNC, SDN and INAH-3, also known as the nucleus of homosexual orientation). Genetically influenced variations, or decreases, of brain aromatase could produce feminization of male sexual preferences, in the absence of estradiol in these key neural regions.

Sexual hormones seem to play an important role in sexual arousal by ensuring cerebral integration between somatic and autonomic sexual systems: they would contribute to the ascent of spinal sexual reflexes to the cerebral level with a consequent erogenization of genital stimulation via activation of autonomic centres. The highest level of sexual arousability is associated with a naturally occurring strong-weak (high-low) ratio of the two antagonist classes of sexual hormones, androgens and estrogens that, acting separately on each of the two antagonist axes (parasympathetic and sympathetic), could induce centrally agonist effects with sex differences in the sexual arousal and response sequence [18, 22, 24, 25].

Androgens

The hypothalamic-pituitary gonadal system is a closed loop feedback control mechanism directed at maintaining normal reproductive function. The gonadal hormones have inhibitory effects on the secretion of LH and FSH. Although testosterone, the major secretory product of testes, is a primary inhibitor of LH secretion in men, other testicular products, i.e. estrogens and other androgens, also inhibit LH secretion. DHT, a non-aromatizable androgen, also inhibits LH secretion. In normal males, 2% of testosterone is free and 30% is bound to sex-hormone binding globulin (SHBG) with high affinity; the remainder is bound with much lower avidity to albumin and this fraction is also available to transfer into target tissue in the brain and liver. Androgens have a key role in both stimulating and maintaining sexual function in man, in particular they are deemed critical for penile tissue development, growth and maintenance of erectile function. However their role in erection and arousal remains controversial. There is growing insight that testosterone has profound effects on tissues of the penis involved in the mechanism of erection as androgen deprivation causes penile tissue atrophy, changes in dorsal nerve structure, changes in endothelial morphology, reduced trabecular smooth muscle content and alterations in extracellular matrix.

In normal adult males there exists wide individual variability in circulating testosterone levels that do not seem to be linked in any meaningful way with individual levels of drive or sexual behavior. It is believed that the level of testosterone required for sexual interest and activity in adult males is lower than normal males' circulating levels of testosterone. Therefore, variability in testosterone levels above this threshold level, or exogenously induced testosterone changes above this level, would not be expected to influence sexual interest or behavior. On the other hand, it is clear that loss of T is associated with loss of

libido. The physiological range of testosterone concentration (3-12 ng/mL) is considerably higher than necessary for normal sexual function. In patients with induced or spontaneous hypogonadism, either pathological withdrawal or re-introduction of exogenous androgens affects the frequency of sexual fantasies, sexual desire and arousal, spontaneous erections during sleep and orgasms.

This physiological underpinning of libido seems to depend on androgenic actions on the paraventricular nucleus of the hypothalamus, an integration centre between the central and peripheral autonomic nervous systems that despite its projections to many important sexual brain areas, controls penile erection [26,27].

Estrogens

Most research suggests that estrogens have little direct influence on sexual desire as, in men, relatively high levels of exogenous estrogen have been somewhat effective in inhibiting sexual desire in sexual offenders. Nevertheless, estrogen is essential for male behaviors. This sexual hormone is usually undetectable in male circulation, thus aromatase-expressing cells in the brain convert circulating testosterone into estrogen, and it is this local estrogen that is thought to control dimorphic behaviors in males. Estrogen mediates many of its effects by signaling through the estrogen receptors ERα and ERβ, which exhibit overlapping expression patterns, and regulate masculinization of the brain and behavior in a complex, redundant manner. The role of a third estrogen receptor, GPR30, in male behaviors is presently unknown [25].

Progesterone

In humans very little research has been conducted on the effect of progesterone on male sexuality, and diverging results have been reported. Progestational drugs such as the antiandrogenically acting progestins medroxyprogesterone acetate (MPA) and cyproterone acetate (CPA) have been successfully used for the treatment of deviant behavior of male sex offenders. Therefore it has been postulated that these drugs can reduce libido through their ability to decrease plasma levels of T [28].

Prolactin

Prolactin hormone (PRL) or luteotropic hormone is synthesized and secreted by sex binding lactotrope cells in the adenohypophysis (anterior pituitary gland). It is also produced in other tissues including the breast, the decidua, parts of CNS, and the immune system. Pituitary PRL secretion is regulated by neuroendocrine neurons in the hypothalamus, the most important ones being the neurosecretory tuberoinfundibular neurons of the arcuate nucleus, which secrete dopamine to act on the dopamine-2 receptors (D2-R) of lactotrophs, causing inhibition of PRL secretion. Thyrotropin-releasing hormone has a stimulatory effect on PRL release. PRL has many effects including regulating lactation, as during pregnancy it causes

enlargement of the mammary glands of the breasts and increases the production of milk, and stimulating proliferation of oligodendrocyte precursor cells.

Moreover, PRL provides the body with sexual gratification after sexual acts: sexual arousal and stimulation per se does not alter prolactin levels significantly but postorgasmic change levels might be of crucial interest for the interpretation of refractoriness and loss of sexual drive. It has been recently hypothesized that PRL may represent a negative feedback mechanism whereby this hormone may modify the activity of dopaminergic neurons in the CNS, especially in the nigrostriatal and mesolimbocortical system and the MPOA, that are regarded as controlling different aspect of sexual behavior. Interestingly, a single case study showed that a multiorgasmic male demonstrated a striking absence of orgam-induced PRL secretion that paralleled an extremely short refractory period.

High PRL blood levels are suspected to be responsible for impotence and loss of libido [29-30].

Oxitocin

Oxytocin (OT) is a mammalian hormone that also acts as a neurotransmitter in the brain. OT is made in magnocellular neurosecretory cells of the supraoptic and paraventricular nuclei of the hypothalamus and it is stored in the posterior lobe of the pituitary gland (neurohypophysis). OT is also made by some neurons in the paraventricular nucleus that project to other parts of the brain and to the spinal cord. Depending on the species, oxytocin-expressing cells are located in other areas, including the amygdala and bed nucleus of the stria terminalis. OT is best known for its roles in female reproduction: it is released in large amounts after distension of the cervix and vagina during labor, and after stimulation of the nipples facilitating birth and breastfeeding, respectively. Recent studies have begun to investigate the role of oxytocin in various behaviors, including social recognition, pair bonding, anxiety, trust, love, maternal behaviors and orgasm. At the level of sexual physiology, OT has been identified as marker of orgasm in humans, with circulating levels significantly increasing around the time of orgasm. OT seems to facilitate sperm transport by increasing smooth muscle contractility in the reproductive tracts. Several animal studies document that OT facilitates penile erection via descending projections from the paraventricular nucleus to the lumbosacral spinal cord as well as decreasing ejaculation latency [31].

Erection

Erection is a neurovascular event characterized by the tumescence of the cavernous bodies that relies upon integration of neural and humoral mechanisms at various levels of the nervous system. It requires the participation of autonomic and somatic nerves and the integration of numerous spinal and supraspinal sites.

Hemodynamic of Erection

The hemodynamic events that maintain penile flaccidity or elicit erection are determined by the tone of penile smooth muscle of the arteries and the trabecular tissue. The contractile activity of this particular muscle is regulated by the balance and interaction between relaxant and contractile factors: hormones, neurotransmitters and endothelium-derived substance. Detumescence of the penis is mediated by adrenergic nerve terminals whose neurotransmitter, noradranaline, activates adrenergic receptors (in particular the alpha-1 higher expressed in the trabecular muscle). Adrenergic stimulation causes vasoconstriction of the penile arteries and contraction of the trabecular smooth muscle respectively resulting in the arterial inflow reduction and in the collapse of lacunar spaces. Endothelin-1, a potent vasoconstrictor peptide synthesized by the endothelium and, probably, by the trabecular muscle itself, is involved in the regulation of contractility of the human cavernous tissue. Many other substances have been found to regulate penis Detumescence so far: several constrictor prostanoids (PGH2, PGF2α, TXA2) are produced by the cavernous tissue and simultaneously released with nitric oxide to attenuate its dilator effect; angiotensin II, maybe through the AT-1 subtype receptor, evokes contraction of corpus cavernosum. Once the penile smooth muscle is activated, various specific signaling mechanisms lead to an intracellular free calcium concentrations increase with the activation of myosin that thereby could be directly activated via Rho-kinase. Vasodilatation is the first event in the development of erection and it is the direct consequence of the increase of blood flow and pressure into lacunar space (see fig 2). The relaxation of the smooth muscle cells depends on endocrine (circulating substance), paracrine (substances released from endothelium and neighboring nerves) and maybe autocrine (substances synthesized by the smooth muscle) mechanisms.

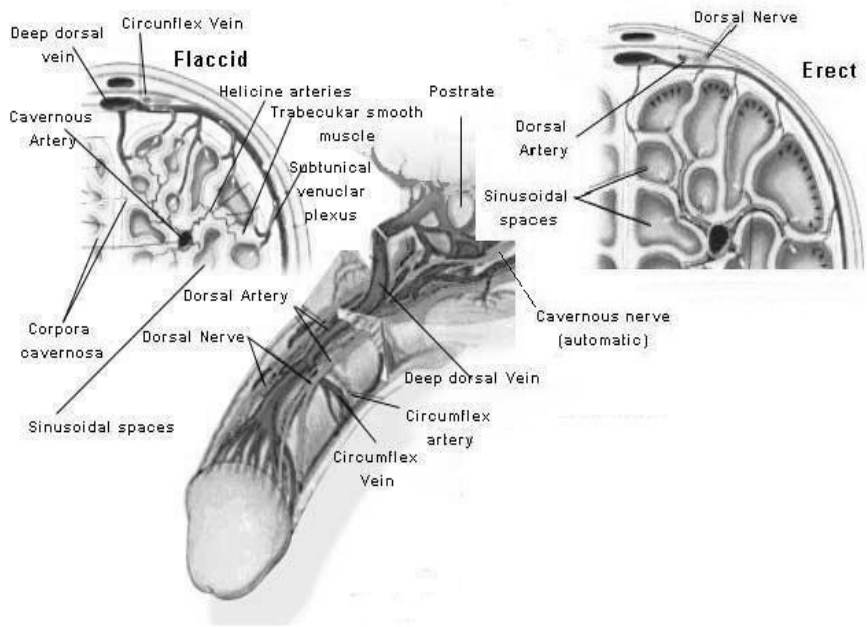


Figure 2 shows neurovascular structures of the penis with sinusoidal space engorgement during erection.

Anywhere, the endothelium itself plays the pivotal role in the process of erection regulating vascular physiology. Endothelium-dependent relaxation of the human corpus cavernosum is mediated only by nitric oxide (NO) while penile arteries dilatation is due both to NO and to endothelium-derived hyperpolarizing factor (EDHF), the latter acting through the opening of the potassium channels. NO is a highly reactive free radical synthesized by the NO synthase (NOS) that uses the amino acid L-arginine and molecular oxygen, in the presence of tetrahydrobiopterin and nicotamide adenine dinucleoside phosphate hydrogen, to produce NO and L-citrulline. There are three different isoforms of NOS: the two constitutive ones, endothelial NOS (eNOS) and neural NOS (nNOS) are respectively present in the autonomic nerves and in the endothelium of the penis while the inducible form (iNOS) is expressed only after exposure to inflammatory mediators. Parasympathetic nerves which release NO as cotransmitter with Ach, are known as nitrergic nerves. The release of NO could be due to the activation of endothelium cells via postganglionic cholinergic nerves, or to the action of circulating plasma substances such as oxygen or bradykinin or, more probably, to the shear stress caused by the expansion of vascular and sinusoidal lumen occurring during erection. Once produced, NO diffuses into the vascular smooth muscle cells adjacent to the endothelium where it binds and activates guanylyl cyclase. This enzyme catalyzes the dephosphorylation of GTP to cGMP, which serves as a second messenger for many important cellular functions, particularly for signalling smooth muscle relaxation. The regulation of the balance between these dilator and constrictor mechanisms is not fully understood involving a complex interaction between nitrergic, cholinergic and noradrenergic neurotransmission. Cholinergic activity in the human corpus cavernosum would have a modulatory role facilitating erection, on the one hand reducing constrictor adrenergic tone and on the other facilitating NO-mediated relaxation.

Moreover noradrenergic responses are under nitrergic control so that even the presence of high noradrenaline concentrations fails to determine an effect when nitrergic neurotransmission is operating [32,33].

Innervation of Penis

The penis receives innervation from sacral parasympathetic (pelvic), thoracolumbar sympathetic (hypogastric and lumbar chain) and somatic (pudendal) nerves (see figure 3). The major excitatory input to the penis is provided by the parasympathetic nervous system, responsible for vasodilatation of the penile vasculature and erection. The preganglionic fibers, originating from the sacral spinal cord (S2-S4), reach the pelvic plexus though the pelvic nerve. The cavernous nerves, exiting the plexus, contain parasympathetic and sympathetic fibers providing the vasodilator and vasoconstrictor input to penile smooth muscle and their course is clinically relevant, as urethral as well as prostatic injury, bladder and rectal surgery can disrupt this nerve and cause erectile dysfunction (ED). Sympathetic preganglionic nerve fibers to the penis originate from neurons located in the 10^{th} thoracic to the 2^{nd} lumbar spinal cord segments. These fibers, after synaptic connections in the sympathetic paravertebral chain ganglia, reach the mesenteric and hypogastric plexus; the resulting hypogastric nerve reaches the pelvic plexus so that the sympathetic outflow to the urogenital area is provided via the pelvic, cavernous and pudendal nerves. Sympathetic nervous system seems to play a pivotal role in the detumescence of the penis. Beyond the autonomic innervations, the penis receives somatic afferents from the dorsal nerve of the penis (DPN), the sensory branch of the pudendal nerve. The sensory innervation of the glans penis is unique as nearly 90% of

afferent terminals are free nerve endings. Afferent input from penile skin, prepuce and glans conveyed by the DNP initiates and maintains reflexogenic erections.

Other afferent fibers, originating in the penile tissue or the urethra, are activated during the filling of the penis with blood or of the proximal urethra with secretion of the sex glands and may elicit and enhance reflexive erection.

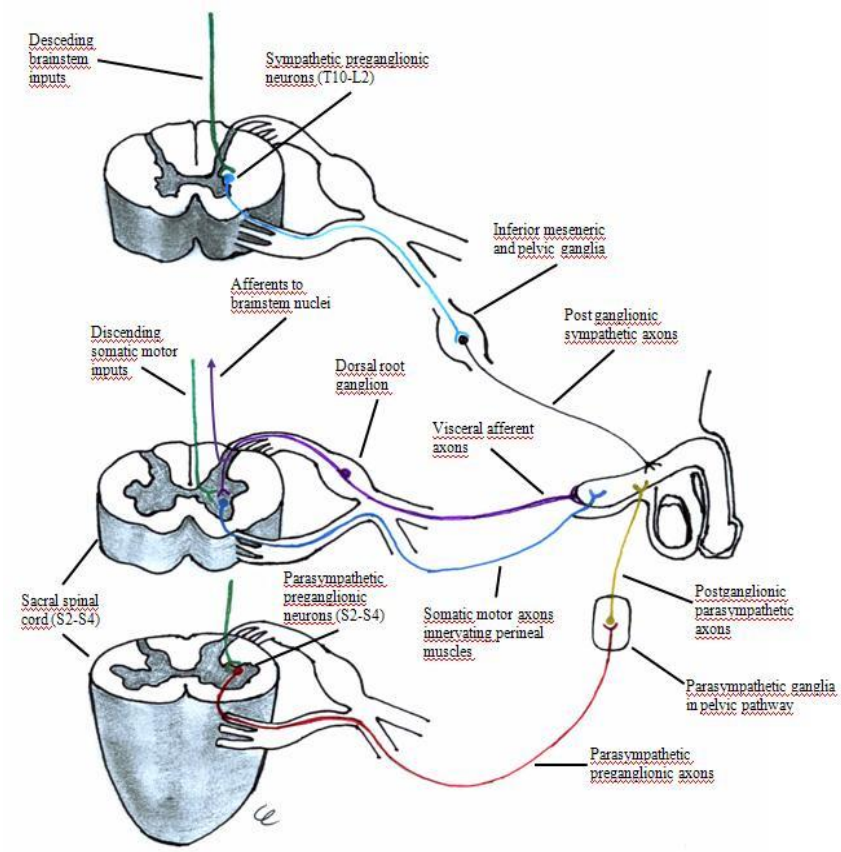


Figure 3 shows parasympathetic and sympathetic innervation of the penis.

Spinal Control

The spinal cord contains the autonomic and somatic nuclei of efferent pathways to the penis and perineal striated muscles. In turn, it receives afferent information both through the somatic and visceral fibers originating from the penis and perigenital area and through the descending projections from several nuclei of the brainstem and hypothalamus. For this reason, spinal cord can be considered the integrative and coordination centre of both reflexive and psychogenic erections. The sacral spinal cord centers are essential for penile erection. Tactile stimulation of the penis or supraspinal stimuli received and originating within the brain can elicit an erection but excitatory and inhibitory mechanisms within the spinal cord integrate these neural inputs so to ensure coordination of sexual reflexes and inhibition of adjacent organ function during sexual activity.

Preganglionic parasympathetic neurons are located in the immediolateral cell column of the sacral spinal cord and contain acetylcholine, NO, VIP, and possibly calcitonin gene

related peptide (CGRP). At this level, in the sacral ventral horn, Onuf's nucleus (S2-S4) is responsible for the somatic innervations of the bulbospongiosus and ischiocavernosus muscles. In contrast to the single spinal origin of the sacral parasympathetic outflow, sympathetic efferent pathways to the abdominal and pelvic viscera and their vascularization take their origin in two different areas of the thoracolumbar spinal cord (the intermediolateral cell column and the dorsal grey commissure of the sole L1-L2 segment) whose hypothesized different function is still unknown.

Sympathetic preganglionic neurons contain a variety of neuromediators colocalized with the classical acetylcholine such as NO, enkephalin, CGRP, somatostatin, neurotensin and substance P and are surrounded by fibers that contain several neuropeptides and glutamate. Activation of sympathetic pathways elicits a clear antierectile effect in some animal species, even if its role has not been so well identified as there are evidences that hypogastric nerves may mediate erections when the sacral cord or pelvic nerve is destroyed. Whatever its context (psychogenic, reflexive or nocturnal) normal erection results from both increased activity of the parasympathetic and decreased activity of the sympathetic autonomic nervous system. A lesion of sacral pathways eliminates the parasympathetic contribution sparing the sympathetic innervation. Thus, a change in the activity of the sympathetic outflow, elicitated by "proerectile" stimuli, allows blood to fill the penis and to generate erection, even if mostly partial [22, 34-37].

Supraspinal Control

Erections occur in response to tactile, visual, imaginative and olfactory inputs and are triggered by supraspinal centers. It is likely that reflexogenic and psychogenic stimuli act synergistically via sacral parasympathetic route. The supraspinal events involved in erectile function are poorly understood and almost based on animal models. Hypothalamic and limbic pathways seem to play a pivotal role in erection with particular regard of MPOA that, beyond erection modulation, coordinate autonomic events associated with sexual response such as increasing in heart rate and cutaneous flushing. Many other supraspinal centers (i.e. dorsomedial and ventromedial and paraventricular hypothalamic nuclei, Barrington's nucleus of the pons, medullary raphe, nPGi, locus ceruleus and periaqueductal gray) and their connection with limbic and cortical areas are involved in erection.

In particular dorsomedial hypothalamic nucleus (DMN) projects to the mesencephalic (fig 2) reticular formation though the central and dorsal gray matter and locus ceruleus. Both DMN and ventromedial hypothalamic nucleus (VMN), descending through the forebrain bundle, mammillary bodies, tegmental regions, substantia nigra and pontine nuclei, reach finally, via the dorso-lateral funiculus of spinal cord, the lumbosacral autonomic centers involved in penile erection. These roots also reach Onuf's nucleus, the sole spinal somatic motor nucleus to receive direct projections from hypothalamus. Interestingly, hypothalamic nuclei receive information directly from genital regions [38-41].

Ejaculation

Ejaculation is a complex and still poorly understood neurological mechanism, at both spinal and cerebral levels as it is closely associated with orgasm which refers to the ejaculation extragenital responses and the subjective pleasurable feelings.

Physiologically ejaculation is defined as the expulsion of seminal fluid from the urethral meatus and consists of two phases: emission and expulsion.

Emission is characterized by the secretion from epithelial cells and the accessory sex glands of seminal fluids, excreted and stored in the proximal urethra. Parasympathetic as well as sympathetic responses are involved, even if emission is mostly considered a sympathetic response. The parasympathetic nucleus (S2-S4) contains visceromotoneurons that control a variety of pelvic organs, including the bladder, penis, urethra and prostate. Emission begins with sensory stimulation of penile afferents (via dorsal nerve of the penis) that lead impulses to the thoracolumbar sympathetic centers of emission (T10-L3). Autonomic sympathetic efferents cause contraction of smooth muscle in the prostate, vas deferens and seminal fluid as well as bladder neck contraction that reaches a pressure up to 500 cmH2O to prevent retrograde flow of the semen into the bladder.

Expulsion is a mixed spinal circuit with parasympathetic afferents, a parasympathetic and somatic spinal centre (Onuf's nucleus) and somatic efferents. It is the result of rhythmic contractions and relaxations of striated perineal muscles, primarily the bulbospongiosus muscle. The onset of expulsion is probably triggered by visceral-sensory inputs, i.e. the deposition of semen in the distal urethra.

Therefore, successful ejaculation depends on coordinated responses involving autonomic (i.e. the synchronized activation of visceral accessory structures such as prostate, sexual glands and tunica albuginea) and somatic (i.e. the rhythmic contraction of perineal and pelvic striated muscles that encompass the participation of several reflexes such as the bulbocarnosus, the abdominal-genital and the ano-cavernosal).

Ejaculation is mediated by a spinal control center, referred as a *spinal pattern generator* (Carro-Juarez 2008), that coordinates sympathetic, parasympathetic and motor (somatic) outflows integrating the latter with the inputs from the supraspinal sites in brainstem, hypothalamus and preoptic area. Interestingly sensory information related to ejaculation is processed in the spinal cord and brain, possibly contributing to the rewarding properties of ejaculation.

A central pattern generator (CPG) is defined as a neural circuit that can produce self-sustained patterns of repetitive rhythmic outputs to the muscles involved in the rhythmic behavior, independently of the sensory input. The complexity of neural motor networks correlates with the complexity of the movement generated by a given CPGs: most basic GPGs coordinate protective reflexes such as swallowing or coughing while the maximum level of complexity is found in those GPGs playing a role in different patterns of goal-directed behaviors (i.e. attack, the search for water and sexual behavior), that are triggered in response to stimulation of higher neural structures such as the hypothalamus or the periaqueductal gray region.

It has been hypothesized that an integral part of the spinal generator for ejaculation is a group of interneurones, located into the lumbosacral spinal cord, which convert sensory signals into motor and autonomic outputs. Thus, a population of interneurons in the central

gray of the lumbar segments L3-L4 that could play a pivotal role in the control of ejaculation has been recently identified. This population consists of cells located in lamina X and VII formally named lumbar spinothalamic cells (LST) as they contain galanin, neurokinin 1, cholecystokinin and enkephalin and send projections to a nucleus located within the posterior intralaminar thalamus, i.e. the parvocellular subfascicular thalamic nucleus. The location of LST in the central gray overlaps with the location of pudendal nerve terminals so that it is thought to be the primary relay of sensory information during summation of sexual activity. In fact, the GPG for ejaculation can be activated by sensory and mechanical stimulation of all those genital structures (penis, scrotal skin and urethra) involved in the stereotyped ejaculatory motor pattern.

The modulatory systems-intrinsic and extrinsic-of CPGs are essential to its operation. The 5HT released by the descending pathways from the brainstem exerts an inhibitory control upon sexual reflexes, including ejaculation, even if 5-HT1A receptors activation facilitates ejaculation. Dopamine facilitates sexual response as activation of D2-like receptors mediates the expulsive phase of ejaculation. Noradrenergic and cholinergic pathways produce facilitation of the ejaculatory pattern and, moreover, ejaculation seems to be enhanced by oxytocin.

It's clear that ejaculation is under CPG control that, in turn, is under descending inhibitory and excitatory influence of supraspinal sites that form a heavily interconnected network and act in concert to regulate sexual behavior. These sites include MPOA and PVN exerting excitatory influence of the spinal ejaculation generator, and nPG1 with a powerful inhibitory influence over the ejaculatory reflexes as the majority of neurons in the nPGi that project to lumbosacral spinal cord are serotoninergic. The MPOA is a key site for male sexual behavior in general, and dopamine in the MPOA appears to facilitate ejaculatory reflexes via D2 receptors. The MPOA does not have direct connections with the lumbosacral spinal cord and instead seems to act via indirect connections with the PVN, that contains the neurotransmitter oxytocin, and with the nPGi.

Other important brain areas that may contribute to the central control of ejaculation include the lateral hypothalamus, the medial amygdale, MEA and BNST.

In short, ejaculation is a spinal reflex controlled by the spinal ejaculation generator, itself modulated by sensory input from the pelvis and descending input from the brainstem and the hypothalamus. These supraspinal centers are in turn controlled by higher centers, referred as cortico-limbic centers that correspond to the psychological control of ejaculation and are notably responsible for switching on the state of sexual excitement [41-51].

Orgasm refers to the subjective experience of pleasure associated with those somatic phenomena occurring during ejaculation such as the rhythmic contractions of the genital and reproductive organs, cardiovascular and respiratory changes and the release of sexual tension [15]. This subjective sensation could be the consequence of both sympathetic and parasympathetic cerebral tension-release processes occurring together. It is important to underline that ejaculation and orgasm can be dissociated in men as the possibility of ejaculation without orgasm (anesthetic ejaculation) has been documented and orgasm can occur without ejaculation ("nonsexual orgasm").

Conclusion

Despite the growing worldwide interest in human sexual behavior, our understanding of this issue is still limited and mostly based on animal studies and few case report or small scaled studies. The current evidences suggest that there is an interconnected neural network where different brain regions and the related phases of sexual response are simultaneously activated, producing the physical and psychological manifestations of human sexuality. In particular the initial phase, i.e. sexual desire, is primarily mediated by subcortical structures, i.e. hypothalamus, ansa lenticularis and pallidum and is regulated by the prefrontal lobe cortex. The temporal lobes, specifically the amigdalae also, play an integral role in regulating human sexual drive. Sexual excitement is mediated by subcortical structures, namely the parietal and frontal lobes, which respectively control genital sensation and the motor aspects of sexual response, sustaining sexual activity until progression to orgasm, for which the septal region has been implicated.

More is known instead about the peripherical structures and neurotransmitters involved in erection and ejaculation, whereas a complex interplay between the sympathetic and parasympathetic autonomic nervous systems have been largely demonstrated.

References

[1] Masters WH, Johnson VE. *Human Sexual Response*. Boston, MA: Little, Brown; 1966.

[2] Kaplan HS. *The New Sex Therapy*. New York, NY: Brunner/Mazel; 1974.

[3] Argiolas A, Melis MR. The neurophysiology of the sexual cycle. *J. Endocrinol. Invest*. 2003;26(3 Suppl):20-2.

[4] Pfaus JG, Kippin TE, Coria-Avila GA. What can animal models tell us about human sexual behavior? *Annu. Rev. Sex. Res*. 2003; 14:1-63

[5] Baird AD, Wilson SJ, Bladin PF, Saling MM, Reutens DC. Neurological control of human sexual behaviour: insights from lesion studies. *J. Neurol. Neurosurg. Psychiatry*. 2007;78:1042-9.

[6] Swanson LW. The neuroanatomy revolution of the 1970s and the hypothalamus. *Brain Res. Bull*. 1999;50(5-6):397.

[7] Brunetti M, Babiloni C, Ferretti A, Del Gratta C, Merla A, Olivetti Belardinelli M, Romani GL. Hypothalamus, sexual arousal and psychosexual identity in human males: a functional magnetic resonance imaging study. *Eur. J. Neurosci*. 2008;27:2922-7

[8] LeVay S. A difference in hypothalamic structure between heterosexual and homosexual men. *Science.* 1991; 253:1034-7.

[9] Paredes RG, Baum MJ. Role of the medial preoptic area/anterior hypothalamus in the control of masculine sexual behavior. *Annu. Rev. Sex Res.*1997;8:68-101.

[10] Baird AD, Wilson SJ, Bladin PF, Saling MM, Reutens DC. The amygdala and sexual drive: insights from temporal lobe epilepsy surgery. *Ann. Neurol.* 2004;55:87-96.

[11] Swanson LW, Petrovich GD. What is the amygdala? *Trends Neurosci.* 1998;21:323-31.

[12] McKenna K. The brain is the master organ in sexual function: central nervous system control of male and female sexual function. *Int. J. Impot. Res*. 1999;11 Suppl 1:S48-55.

[13] Pfaus JG. Pathways of sexual desire. *J. Sex Med*. 2009; 6:1506-33.
[14] Motofei IG. A dual physiological character for sexual function: libido and sexual pheromones. *BJU Int*. 2009; 104:1702-8
[15] Motofei IG, Rowland DL.The physiological basis of human sexual arousal: neuroendocrine sexual asymmetry. *Int. J. Androl*. 2005; 28:78-87.
[16] Devidze N, Lee AW, Zhou J, Pfaff DW.CNS arousal mechanisms bearing on sex and other biologically regulated behaviors. *Physiol. Behav*. 2006;88:283-93.
[17] Ferretti A, Caulo M, Del Gratta C, Di Matteo R, Merla A, Montorsi F, Pizzella V, Pompa P, Rigatti P, Rossini PM, Salonia A, Tartaro A, Romani GL. Dynamics of male sexual arousal: distinct components of brain activation revealed by fMRI. *Neuroimage*. 2005 15;26:1086-96.
[18] Meston CM, Frohlich PF. The neurobiology of sexual function. *Arch. Gen. Psychiatry*. 2000 ;57:1012-30
[19] Hull EM, Muschamp JW, Sato S. Dopamine and serotonin: influences on male sexual behavior. *Physiol. Behav*. 2004; 83:291-307.
[20] Dominguez JM, Gil M, Hull EM. Preoptic glutamate facilitates male sexual behavior. *J. Neurosci*. 2006; 26:1699-703.
[21] Van Furth WR, Wolterink G, van Ree JM. Regulation of masculine sexual behavior: involvement of brain opioids and dopamine. *Brain Res. Rew*. 1995;2:162-84.
[22] Bancroft J. Biological factors in human sexuality. *J. Sex Res*. 2002;39:15-21.
[23] Zhou J, Lee AW, Devidze N, Zhang Q, Kow LM, Pfaff DW. Histamine-induced excitatory responses in mouse ventromedial hypothalamic neurons: ionic mechanisms and estrogenic regulation. *J. Neurophysiol*. 2007;98:3143-52.
[24] Lewis RW, Mills TM. Effect of androgens on penile tissue. *Endocrine*. 2004;23:101-5.
[25] Wu MV, Manoli DS, Fraser EJ, Coats JK, Tollkuhn J, Honda S, Harada N, Shah NM. Estrogen masculinizes neural pathways and sex-specific behaviors. *Cell*. 2009;139:61-72.
[26] Morales A, Buvat J, Gooren LJ, Guay AT, Kaufman JM, Tan HM, Torres LO. Endocrine aspects of sexual dysfunction in men. *J. Sex Med*. 2004;1:69-81.
[27] Morales A, Black A, Emerson L, Barkin J, Kuzmarov I, Day A. Androgens and sexual function: a placebo-controlled, randomized, double-blind study of testosterone vs. dehydroepiandrosterone in men with sexual dysfunction and androgen deficiency. *Aging Male*. 2009; 12:104-12
[28] Andersen ML, Tufik S. Does male sexual behavior require progesterone? *Brain Res. Rev*. 2006;51:136-43.
[29] Krüger TH, Haake P, Hartmann U, Schedlowski M, Exton MS. Orgasm-induced prolactin secretion: feedback control of sexual drive? *Neurosci. Biobehav. Rev*. 2002;2:31-44.
[30] Krüger TH, Haake P, Chereath D, Knapp W, Janssen OE, Exton MS, Schedlowski M, Hartmann U. Specificity of the neuroendocrine response to orgasm during sexual arousal in men. *J. Endocrinol*. 2003;177:57-64.
[31] Argiolas A, Gessa GL. Central functions of oxytocin. *Neurosci. Biobehav. Rev*. 1991 ;15:217-31.

[32] Sáenz de Tejada I, Angulo J, Cellek S, González-Cadavid N, Heaton J, Pickard R, Simonsen U. Physiology of erectile function. *J. Sex Med.* 2004;1:254-65.

[33] Maas R, Schwedhelm E, Albsmeier J, Böger RH. The pathophysiology of erectile dysfunction related to endothelial dysfunction and mediators of vascular function. *Vasc. Med.* 2002;7:213-25.

[34] Giuliano F, Rampin O. Neural control of erection. *Physiol. Behav.* 2004; 83:189-201.

[35] Lepor H, Gregerman M, Crosby R, Mostofi FK, Walsh PC. Precise localization of the autonomic nerves from the pelvic plexus to the corpora cavernosa: a detailed anatomical study of the adult male pelvis. *J. Urol.* 1985;133:207-12.

[36] Marson L, Platt KB, McKenna KE. Central nervous system innervation of the penis as revealed by the transneuronal transport of pseudorabies virus. *Neuroscience.*1993; 55:263-80.

[37] Schmidt MH, Schmidt HS. The ischiocavernosus and bulbospongiosus muscles in mammalian penile rigidity. *Sleep.* 1993;16:171-83.

[38] Marson L, McKenna KE. Serotonergic neurotoxic lesions facilitate male sexual reflexes. *Pharmacol. Biochem. Behav.* 1994;47:883-8.

[39] Sachs BD. Placing erection in context: the reflexogenic-psychogenic dichotomy reconsidered. *Neurosci. Biobehav. Rev.* 1995;19:211-24.

[40] Rajaofetra N, Passagia JG, Marlier L, Poulat P, Pellas F, Sandillon F, Verschuere B, Gouy D, Geffard M, Privat A. Serotoninergic, noradrenergic, and peptidergic innervation of Onuf's nucleus of normal and transected spinal cords of baboons (Papio papio). *J. Comp. Neurol.* 1992; 318:1-17

[41] Steers WD. Neural pathways and central sites involved in penile erection: neuroanatomy and clinical implications. *Neurosci. Biobehav. Rev.* 2000; 24:507-16.

[42] Motofei IG. A dual physiological character for sexual function: the role of serotonergic receptors. *BJU Int*. 2008;101:531-4.

[43] Coolen LM. Neural control of ejaculation. *J. Comp. Neurol*. 2005;493:39-45.

[44] Coolen LM, Allard J, Truitt WA, McKenna KE. Central regulation of ejaculation. *Physiol. Behav*. 2004;83:203-15.

[45] Carro-Juárez M, Rodríguez-Manzo G. The spinal pattern generator for ejaculation. *Brain Res. Rev.* 2008;58:106-20.

[46] Allard J, Truitt WA, McKenna KE, Coolen LM. Spinal cord control of ejaculation. *World J. Urol*. 2005; 23:119-26.

[47] Guertin PA, Steuer I. Key central pattern generators of the spinal cord. *J. Neurosci. Res.* 2009; 87:2399-405.

[48] Motofei IG, Rowland DL. Neurophysiology of the ejaculatory process: developing perspectives. *BJU Int.* 2005;96:1333-8.

[49] Giuliano F, Clement P. Neuroanatomy and physiology of ejaculation. *Annu. Rev. Sex Res*. 2005;16:190-216.

[50] Peeters M, Giuliano F. Central neurophysiology and dopaminergic control of ejaculation. *Neurosci. Biobehav. Rev*. 2008;32:438-53.

[51] Giuliano F, Clément P. Physiology of ejaculation: emphasis on serotonergic control. *Eur. Urol.* 2005;48:408-17.

In: Male Sexual Dysfunctions in Neurological Diseases… ISBN 978-1-61761-855-0
Editor: Calabrò Rocco Salvatore

Chapter 2

Psychological Aspects of Human Sexuality

Jacopo Grisolaghi, Fabrizio Quattrini and Rocco Salvatore Calabrò

Abstract

From the past decades, there has been growing evidence for an important psychological role in human sexual behavior. Evidence that the development of gender identity, gender role and sexual orientation plays an essential role into the definition of Self comes from many studies. There is also evidence that patient-perceived sexual changes after neurological diseases play a key role in well-being. Social and psychosocial factors, including cognitive and emotional resources, can engender different outcome in the development and realization of sexual identity and behavior, especially when a coherent body image is not experienced. The explication of sexuality is seen as an important component of people's social ecology. The present chapter provides a conceptual link between the goals of the psychosexual development and the psychotherapy intervention when it is required. The authors argue that sexuality, as a normative part of human development, culture, identity, and relationships, should be approached from an asset-based perspective, rather than a deficit-based perspective. We debate the complex and self-perceived aspects of sexuality in people's lives. We also propose a framework that illustrates how aspects of sexuality are embedded within contexts life, and describe how an opportune sexual psychological treatment program, rooted in WHO guidelines, can help people to improve their well-being.

Introduction

The present chapter represents a brief picture of the importance of psychological aspects in human sexuality, namely a wide range of behavioral processes including physiological, cultural, and psychological aspects of sex. Human sexuality is often defined as the quality or state of sexual being that relates to an individual’s need for caring, closeness, and affection.

Sexual function is a legitimate aspect of medicine, defined by the World Health Organization (WHO) declaration of sexual rights: "Sexual rights…include the right of all individuals…to (achieve) the highest attainable standard of sexual health…and to pursue a satisfying, safe and pleasurable sexual life." Sexuality is an essential part of human development, and it is not limited to sexual intercourse, but covers a wide range of behaviors, personal expression and communication (Savin-Williams and Diamond, 2004). Beyond the physical experience of a changing body, sexuality and gender identity and their expression affect people's intrapersonal, relational, and societal interactions. There are numerous psychological factors which influence sexuality. Evolutionary psychology emphasizes that universal mental adaptations will sometimes be sex specific in design because males and females, consistently throughout human evolutionary history, faced sex-specific adaptive problems in the domain of sexual matters (Symons, 1995). For the purposes of this book we will focus particularly on the psychological aspects of human sexuality which are involved in neurological diseases. To introduce the topic it is important to remember that sexual behavior is highly affected by social norms and the culture which surrounds us. For example mass media play a large role in establishing and molding the norms that society chooses. The factors emphasized by these societal norms can have tremendous impact on the psychology of people. Men may experience depression, anxiety, lack of sex drive, and loss of confidence as a result of their inability to meet society's expectations.

In addition, it is important to underline the possible embarrassment, and the uneasiness that people often feel whenever there is a discussion about sex. This difficulty could be due to the inability to express in words this particular knowledge as it is rooted in our emotions and body.

The discomfort and the embarrassment could increase in situations where the speakers have a handicap in expressing themselves, as it could be difficult to imagine what sensations are included in the speaker's idea of sexuality (Veglia, 2000).

1. Gender Identity, Gender Role and Sexual Orientation

The human psychosexuality could be understood and determined by the explanation of three variables: gender identity, gender role and sexual orientation (Zucker and Bradley, 1995). The gender role, a term introduced by Money (1975), refers to what a person says and does to indicate to himself and others the degree of his femininity, masculinity or ambivalence, including sexual response and excitement. Hence, the gender role is sort of an external expression of gender identity, in other words the way a person displays himself reflects directly or indirectly the behaviors that are suggested by his society and culture at that current moment (Gagnon and Simon, 1973). Masculine and feminine stereotypes represent the general consent regarding the assigned roles to men and women, to sons and daughters and these constitute the matrix which shapes our personal scheme of masculinity and femininity (Money, 1994). Therefore the stereotype, from which we obtain consent for our gender identity, must be rigid enough to give us certainty, but at the same time must be sufficiently flexible so that whenever it changes it is not traumatic for us. This is perfectly

applicable in a society like ours, in which we are seeing profound changes of what it means to be a man or a woman (Dèttore, 2005).

We commonly refer to gender role when considering behaviors, attitudes and personal traits that a society, in a specific culture and historical moment, indicates as masculine or feminine and as more fitting to the masculine or feminine role (Huston, 1983). Therefore, every society can define arbitrarily its own gender roles.

Since the 1970s gender identity – a term distinct from gender role – indicates the sense of Self, the unity and the persistency of masculine, feminine or ambivalent individuality. Using Money's (1975) words, it is the personal experience of the gender role, indicating the sense of Self as male or female. Indeed, the gender identity creation process occurs when the four stages from conception to language learning are completed. The first stage refers to the fecundation, in which the sperm holding X or Y genome results in a male or female chromosome.

The second stage is around the end of the sixth week when, if the fetus is a holder of Y genome, the gonads become testicles. If the process continues in a feminine way, the Müllerian structure will develop into the uterus, the Fallopian tubes and the vagina. With the development of the testicles, the production of androgenic hormones, responsible for the development of the Wolffian duct and the regression of the Müllerian duct starts. If the fetus holds female chromosomes, the third stage will start; in this phase the absolute absence of androgenic hormones is essential. Once birth occurs, the three stages are completed. The fourth and last stage is the psychological one and it is essential for the gender identity; this stage will end all almost around three years. Whilst learning the language, the child will conclusively structure his gender identity by defining himself as male or female. It is necessary for a person to develop inner models of belonging to a sex rather than another. These models are learned from infanthood by observing others' behavior, from the education received and from experiences (Simonelli, 1996). The third pole which determines the human psychosexuality is sexual orientation that is the response modality of the person to various sexual stimuli. Sexual orientation usually manifests through intense attraction and emotional elation towards another person or thing. If the subject feels attraction for a person of the opposite sex, then it has a heterosexual orientation; if it is attracted to people belonging to the same sex, then it has homosexual orientation; if there is an attraction for people from both sexes, the person is said to be bisexual. Moreover, if the subject obtains sexual excitement from objects, people belonging to prepubescent age, inflicting and/or receiving pain, or in other similar situations, the orientation is called paraphilic. It is important to specify that a homosexual person, as Dèttore (2005) suggested, is not characterized by any particular condition of gender identity.

Homosexual men, as well as homosexual women, are happy to be men/women and they feel like men/women; they do not consider or have the need to show behaviors belonging to the other sex.

According to a classical division suggested by others, such as Bancroft (1989), the sexual development could be subdivided into eight levels of expression and definition of gender and sex: sexual chromosomes; presence of the feminine or masculine gonads; hormonal component; internal reproductive structures; sexual external organs and secondary features; assigned gender at birth; gender identity and sexual differentiation of the brain.

The first seven levels follow one after the other; the eighth develops in parallel with the others starting from the third level. As widely documented (2005), gender identity could be

considered as the result of the action of all the previous levels, demonstrating a clear example of the collaboration between nature and culture. Perceiving and interpreting the external stimuli the subject will elaborate his/her own peculiar gender identity which they will express externally in the gender role. Almost all men feel that they are men and their behavior is in accordance with the masculine role: society perceives them as men and they are attracted to partners belonging to the opposite sex. The same thing is applicable to the majority of women. However, gender role, identity role and sexual orientation are not always in agreement.

In this last example, we have various combinations among these components, which should be considered a continuum and not static, as specified in the following classification:

- person with gender identity congruent to his own chromosomal and phenotypical sex and with hetero/homo/bisexual or paraphilic orientation;
- person with identity not congruent with his chromosomal sex but congruent with his own phenotypical and hetero/homo/bisexual or paraphilic orientation, as in the syndrome of insensitivity to androgens or in the androgenital syndrome;
- person with gender identity congruent with his own chromosomal sex but not congruent with his own phenotypical sex and with hetero/homo/bisexual or paraphilic orientation, as in the Turner or Kleinfelter syndrome;
- person with gender identity not congruent with his own chromosomal and phenotypical sex and with hetero/homo/bisexual or paraphilic orientation, as in subjects with gender identity disorder, transsexual or other trans-gender manifestations.

These components constitute one part of the individual's personality and therefore do not label the whole person (2001). Through the famous Kinsey Scale, where the extremes are more theoretical than real, Kinsey et al. suggested that sexual orientation should be evaluated in a dichotomic way but in a continuum (Kinsey, Pomeroy and Martin, 1948). In this sense, with regards to homosexuals, we should also discuss about those individuals who are on the borderline of heterosexuality and vice versa. Many authors, and among them Brancroft (1972) identified countless mistakes in Kinsey classification, first of all the fact that it does not take into consideration the identity and gender role concepts and the feedback the subject gets from the relationships it has with the external environment. Doorn et al. (1994) conceptualized this within a cognitive model; an evolution model related to the gender identity concept would be understandably more effective whether conceived within a Self system. Based on these researches (Doorn *et al*., 1994) the coexistence of two gender identity subsystems, masculine and feminine, has been underlined. The expression of a person's gender identity depends on the strength or dominance of one of the two subsystems or from the intensity, the frequency and the occasions on which one or the other is expressed, as Dèttore (2005) suggests.

As previously quoted (Dèttore and Fuligni, 1999; Dèttore, 2001), the concept of gender identity could be considered a partial aggregate, a subsystem, in terms of Self system organization. The Self system organization is constituted by a variable number of Self versions related to various components of the sexual characterization (orientation, sexual

preferences, information processing, tastes, habits, social rules, etc.). The person's gender identity is derived from this multiplicity of elements (Déttore, 2005).

2. Cognition, Emotions and Sexual Behaviour

The following paragraph will better explain the possible hypotheses of intervention. A typical feature of psychosexual analysis of the human being has been consolidated in the last twenty years, i.e. the integration of different psychotherapeutic models, from psychodynamic to humanistic- experiential and from behavioral to psycho-bodily. Notwithstanding, for a more summarized and narrow research, the present paragraph will undertake some of the most psychological aspects linked to human sexuality from a cognitive-behavioral point of view. As confirmed by recent researches in evidence-based psychotherapy, many authors have undertaken the psychological analysis of human sexuality from a cognitive-behavioral stance (Kendall and Hollon, 1979; Epstein, Schlesinger and Dryden, 1988; Dèttore and Fuligni, 1999; Dèttore, 2005).

From this perspective, the action of a subject is considered the response to a cognitive and behavioral stimulus. We can find the origin of these stimuli respectively as in the imaginary, in proprioception – that could derive from autoperception of one's own physiological processes – as in the environment in which the individual is immersed. Subsequently, the responses delivered could be tracked in the electrocortical activation (cognitive response), in the activation of limbic and neurovegetative systems (emotional response) and in motor activation of skeleton muscles (behavioral response). The interaction of these three components, inserted inside a feedback system, triggered and regulated by innate biological mechanisms and attitudes, expectations and learned values, determines the response acted by the individual.

Observing the human sexuality from this perspective, it appears that the human being, originating from an innate organic base, emits his behavior through diverse processes of learning, distinguishable in three distinctive categories of classical conditioning, instrumental conditioning and shaping (Dodson, 2002; Dèttore, 2005). These ways of learning and their subsequent behavioral modifications, partially depend on the evaluation carried out by the individual with regards to whether it could do a particularly successful action. An important psychological construction that has a central role in this conceptual scheme is self- efficacy (Bandura, 1969, 1977a, 1977b, 1977), considered fundamental for an adequate functioning and the acquisition of the sense of competency.

As illustrated by Dodson (2002) and according to Bandura (1997) the efficacy expectancies are composed of information derived from four primary sources: performance abilities, vicarious experience, verbal belief and the individual's psycho-emotional condition at the moment of the behavior. The direct experience of the behavior and the situation represents one of the main information sources in which the efficacy expectation could be based on. Then, the obtained successes, with the causality attributions (internal or external; stable or non-stable), could raise the efficacy expectations whereas the failures could lower them down.

Beside the variables already examined, it is essential to underline the importance exerted by social comparison, physiological arousal perception and emotional states. This

physiological activation could interfere with the performance and with the threshold vulnerability generating an influence on the efficacy judgment. Every time an individual is going to start a functional behavior (Salovey and Birnbaum, 1989), including sexual behavior, a positive feeling could increase efficacy judgment, as well as a negative feeling could compromise such judgment (Dodson, 2002).

A person with self-efficacy dysfunction could be afraid of starting something new for fear of failure, hence exasperating his low self-esteem. It has been well illustrated (Dèttore, 2005) that the development of both gender and role identity is fundamental; these two aforementioned aspects of the human psychosexuality are linked to the establishment of sexual orientation. Another psychological resource connected to the cognitive sphere, that has a role in many expressions of human sexuality, can be identified in the problem-solving ability, particularly every time a person tries to identify and discover the effective and adaptive solutions to apply to specific problems. The problem-solving ability is considered a conscious and rational activity, which identifies the research process solution towards achieving an objective (Goldfried and Sobocinski, 1975), as sexual intercourse. Moreover, in connection with these abilities, Rotter (1966) has introduced the term 'locus of control' to distinguish among people who think they can manage their own destiny (internal locus of control) and the people who consider their own destiny determined by external factors (Strickland, 1988). Many studies have demonstrated that the internal attribution of causality predisposes to face a wide range of problematic situations, and, therefore, the locus of control is important in human sexuality. As we have seen so far, from a psychological point of view, there are numerous aspects that play a role in sexuality. Some authors refer to the way people see themselves, that subsequently depends largely on their behaviors and actions. Indeed, Bem (1974) has developed the "autoperception theory", which is very important in everyday life as well as in the sexual sphere. Following these studies, Moghaddam (2002) have underlined that when a person has confused signals or difficulty in interpreting his internal being, what he feels and thinks is explained by observing his behavior. Rhodewalt and Agustsdottir (1986) conducted a self-esteem study: participants of a group were persuaded to speak about themselves in a laudatory way, whilst participants of another group were asked to use a more modest language to describe themselves. The first group, after the self-esteem evaluation was completed, obtained higher values, indicating to the researchers the influence that positive language could have on Ego reinforcement.

In order for this effect to be produced, the person should be uncertain about this particular aspect of the Self, and has to believe that the behavior is not forced by the situation (Fazio, 1987).

It is commonly suggested by many researchers that the cognitive evaluation aspects (appraisal) are connected to emotions (Frijda and Zammuner, 1992; Smith, Griner, Kirby and Scott, 1996). In particular, they argue that diverse emotions are connected to different evaluation profiles. It is clear to the reader that emotions may influence both the sexual response – for example a higher activation could disorganize the physiological systems – and the affective response. According to many researchers, mainly the evolutionary theories supporters (Ekman, 1992), emotions might be innate and relatively few, i.e. from six to ten, and might constitute a distinct entity at an expressive, physiological, motivational and experience level. However, according to constructivist theories, emotions may not have a biological origin, rather a cultural one, depending substantially on the language and values

structure of society. In Armond-Jones's opinion (1986), emotions would be infinite or vary according to cultures.

3. Psycho-Sexual Approach Intervention

Nowadays many authors think that clinical intervention should respect the psychosomatic and somatic/psychological setting (Simonelli *et al*., 2010).

When we talk about sexual dysfunctions, we have to take into consideration the possible etiological factors i.e. biological, chemical, physical, psychological and cultural ones, not only in their peculiarity, but in their reciprocal interactions (Simonelli, 2002). Within this conceptualization, the somatic/psychological component enlarged the previous background, suggesting the clinician should bear in mind all the psychological repercussions that could be associated with sexual symptoms with an organic etiology (Borras-Valls and Gonzales-Correales, 2004). For example, we can consider the case of a man who suffers from erectile dysfunction caused by a serious vascular problem. In this specific condition we should not be surprised if he experiences inadequacy, anxiety, dysthymia and more importantly, frustrated feelings relating to his masculine sexual identity.

As suggested by Simonelli (2002), it is necessary for the clinician to take into account both the mind and the body of the individual during the evaluation process, considering the relationship between these two elements, evaluating if the subject is single or in a stable relationship, and contextualizing it all within his particular socio-cultural context. These requirements enable integration within a unique intervention approach of diverse theories and clinical instruments – from sexual counseling to cognitive behavioral psychotherapy, psychodynamic and relational systemic, and from psycho body relaxation to pharmacotherapy, just to mention a few – in order to single out effective levels of intervention suitable to the person's needs (Rossi, Michetti and Simonelli, 1998; Ramsay, 2001). With regard to a patient who reports sexual symptoms, the use of the aforementioned approach is outlined as a response, not intended as a technique but "as order of problems asked from users" (Carli, 1998), flexible, effective and complete towards a question sometimes confused that intermingles biological, psychological and relational approaches (Cociglio, 2002). This integrated intervention is mainly used as a therapy for couples, although it is also feasible on singles. In the integrated sexual approach there are four levels of integration to consider: the integration within the therapist's mind, the integration among instruments, integration among models and practitioners.

Integrated models predict the creation of a type of setting in which it is possible to introduce elements belonging to different subjects and to perform within a team composed of diverse professional figures, who are able to speak the same language (Cociglio, 1998). This model of multidisciplinary integration implies that the practitioner and the psychologist take part in the diagnostic process of the patient from the beginning, by evaluating simultaneously the mental and somatic aspects (Stief and Hartmann, 2003). In the last years the sexual interventions are influenced by the change that sexology has undergone after the discovery of medicine in the treatment of erectile dysfunction.

Such a component allowed the creation of a close relationship between the medical and the psychological interventions, underling more markedly the necessity of a multidisciplinary approach to the care and treatment of these disorders, therefore making team work essential.

From the analysis of the contemporary literature and thanks to the experience developed at the Italian Institute of Scientific Sexology (Rome), the authors of the present chapter put forward the following therapeutic steps.

In the first step in this process, for which we would allocate about four meetings, lots of importance is given to the investigation of the specific nature of the problem the couple or the single person is experiencing. At this phase, if the case problem involves a couple, it would be very useful to meet both partners at the same time; rather than meet them as individuals. In order to have a good diagnosis of the sexual dysfunction it would be essential that the psycho-sexologist investigate the accompanying sexual responses as subjective feelings, and also obtain as much information on the sexual history, the relation, the psychic and the emotional well-being of everyone. At the same time the sex consultant, through objective exams, will explore the biological aspects of the problem and the general health of the patient. The examination of the motivations to a possible therapeutic process and the expectations knowledge could enlighten the sexual education received as well as the attitudes and the opinions regarding sex and sexuality of the individuals that will undertake the journey.

The restitution to the patient –usually given at the conclusion of every single interview as at the end of this first phase – will be necessary in order to convey to the individual the feeling of being understood and also to add further information and elements that could be useful to the practitioner. The usage of psychometric instruments will be useful in this diagnostic process, beyond the interview. In fact, an accurate diagnosis will give the opportunity to create a more suitable therapeutic proposal – which would be formulated in a particular session – or refer the patient to another therapeutic practitioner.

At this moment – to conclude the assessment phase previously described – if an emphatic and trustful climate has been established, the patient will be able to choose among the team's suggestions. As previously mentioned, one of the proposals could also be a pharmacological treatment; however the clinician should not fail to pay attention to the psychological and relational aspects too.

In some cases, after the assessment phase, we recommend the patients should undertake sexual counseling for a brief period – in line with WHO and the World Association of Sexology - : this is intended as a support intervention with the aim of developing awareness, based on the patients' resources, in order to improve their quality of life (Simonelli, 2002). In other situations, psychotherapy sessions could be advised, generally characterized by sexual tasks: that is a sort of protocol or prescription of sexual activities, in order to get and reduce anxiety; the single patient or the couple will undertake these tasks at home and then they will discuss it during the following session.

Many aspects of the psycho-relation could have a role in this phase; different moods of the sexual symptoms within the couple, point of strength and weakness, the expression of one's own sexuality and psychological and physical intimacy, just to mention a few. The work on the cognitive, emotional and relational aspects of the proposed therapeutic process requires an effort and a continuous attention by the clinicians, considering that a fixed protocol with an established intervention sequences does not exist. The mentioned flexibility constitutes certainly a strong point in the psycho-sexual intervention, as it gives the clinician the possibility of adapting time to time diverse techniques suitable to the patient's needs.

4. Sex Counseling in Neurological Diseases

Sexuality is one of the most complex aspects of human life. Sexual expression is dependent on functioning anatomical and physiological systems, which are influenced by cognitive and emotional processes. Other than in masturbation and fantasy, sexual expression occurs within the context of a dyadic relationship. To assess and treat problems in this area requires knowledge of those factors influencing both the dynamics of the relationship and the physical and psychological aspects of sexual functioning.

Neurological disease and trauma have long been recognized as causing sexual dysfunction.

Nevertheless, practising neurologists have not traditionally paid much attention to sexual dysfunction in their patients, partly because therapeutic possibilities were scant. With emerging awareness of the primary importance of quality of life as the most important indicator of good patient management, and with the advent of more effective treatment of sexual dysfunction ignoring this very important dimension of life is no longer acceptable. From the sexological point of view, the case history should define the patient's sexual expectations, needs and behavior, and should identify sexual problems as well as misconceptions. Psychological factors are frequently involved, either as an emotional reaction to sexual dysfunction or as a consequence of a socially or physically disabling disease. Dependence and lack of acceptance of the sexual disorder by the patient or the partner, self-perceived unattractiveness and reduced self-esteem also play a relevant role. It is also important to interview the partner (if the patient has one) and to evaluate the quality of the marital/partner relationship.

To summarize, it is important to clarify the nature and the characteristics of sexual dysfunction, to discover any underlying (and possibly treatable) organic cause and to document the existence of primary or secondary psychological factors.

References

Armond-Jones, C. (1986). The tesis of constructionism. In R. Harrè (Ed.) *The social construction of emotion* (pp.32-56). Oxford: Blackwell.

Bancroft, J. (1972). The relationship between gender identity and sexual behavior: some clinical aspects. In C. Ounsted and D.D. Taylor (Eds.) *Gender differences: their ontogeny and significance.* Edimbourgh: Churchill Livingstone.

Bancroft, J. (1989). *Human sexuality and its problems.* Edinbourgh: Churchill Livingstone.

Bandura, A. (1969). *Principles of behavior modification.* New York: Holt, Rinehart and Winston.

Bandura, A. (1977a). Self-efficacy: Toward a unifying theory of behavioral change. *Psychological Review, 84*, 191-215.

Bandura, A. (1977b). *Social learning theory*. Englewood Cliffs, New Jersey: Prentice-Hall.

Bandura, A. (1997). *Self-efficacy: The exercise of control*. New York: Freeman.

Bem, S. L. (1974). The measurement of psychological androgyny. *Journal of Consulting and Clinical Psychology, 42*, 155-162.

Borras-Vallas, J.J., and, Gonzalez-Correales, R. (2004). Specific aspects of erectile dysfunction in sexology. *International Journal of Impotence Research, 16*, S3-S6.

Carli, R. (1998). L'analisi della domanda in sessuologia. In C. Simonelli (Ed.) *Sessualita' e Terzo Millennio, Voll. II*. Milano: Franco Angeli.

Cociglio, G. (1998). L'approccio integrato in sessuologia. *Rivista di Sessuologia Clinica, 2*, 15-25.

Cociglio, G. (2002*). Il Manuale del Consulente Sessuale*. Milano: Franco Angeli.

Dèttore, D. (2001). *Psicologia e psicopatologia del comportamento sessuale.* Milano: McGraw-Hill.

Dèttore, D., and Fuligni, C. (1999). *L'abuso sessuale sui bambini. Valutazione e terapia delle vittime e dei responsabili*. Milano: Mc Graw-Hill.

Dèttore, D. (2005). *Il Disturbo dell'Identità di Genere. Diagnosi, eziologia e trattamento.* Milano: McGraw-Hill.

Dodson, K.S. (2002). *Psicoterapia cognitivo-comportamentale*. Milano: McGraw-Hill.

Doorn, C.D., Poortinga, J., and Verchoor, A.M. (1994). Cross-gender identity in transvestites and male transsexuals. *Archives of Sexual Behavior, 23*, 185-202.

Ekman, P., (1992). An argument for basic emotions. *Cognition and Emotion, 6*, 169-200.

Epstein, N, Schlesinger, S.E., and Dryden, W. (1988). *Cognitive behavioral therapy with families.* New York: Brunner/Mazel.

Fazio, R.H. (1987). Self-perception theory: A current perspective. In M.P. Zanna, J.M. Olson and C.P. Herman (Eds.) *Social Influence: The Ontario Symposium, 5*, 129-149. Hillsdale, NJ: Lawrence Erlbaum.

Frijda N., and Zammuner V.L. (1992). L'etichettamento delle proprie emozioni. *Giornale Italiano di Psicologia, XIX, 3*, 389-423.

Gagnon, J.H., and Simon, W. (1973). *Sexual conduct.* Chicago: Aldine.

Goldfried, M., and Sobocinski, D. (1975). Effects of irrational beliefs on emotional arousal. *Journal of Consulting and Clinical Psychology, 43*, 504-510.

Greenstein A, Abramov L, Matzkin H, Chen J. (2005), "Sexual dysfunction in women partners of men with erectile dysfunction", Int. J. Impot. Res., 18 (1): 44-6.

Huston, A.C., (1983). Sex typing. In E.M. Hetherington (Ed.) *Handbook of Child Psychology: Socialization, Personality and Social Development*. New York: Wiley.

Kendall, P.C., and Hollon, S.D. (1979). *Cognitive-behavioral interventions. Theory, research and procedures.* New York: Academic Press.

Kinsey, A.C., Pomeroy, W.B., and Martin, C.E. (1948). *Sexual Behavior in the Human Male.* Philadelphia: Saunders.

Moghaddam, F.M. (2002). *Psicologia Sociale*. Bologna: Zanichelli.

Money, J. (1975). Ablatio penis: Normal male infant sex-reassigned as girl. *Archives of Sexual Behavior, 4*, 65-71.

Money, J. (1994). The concept of gender identity disorder in childhood after 39 years. *Journal of Sex and Marital Therapy, 20*, 163-177.

Ramsay, R. (2001). The clinical challenger of assimilative integration. *Journal of Psychotherapy Integration, 11, (1)*, 21-42.

Rhodewalt, F., and Agustsdottir, S. (1986). The effects of self-presentation on the phenomenalself. *Journal of Personality and Social Psychology, 50*, 47-55.

Rossi, R., Michetti, P. M., and Simonelli C. (1998). L'approccio integrato nell'esperienza dell'Istituto di Sessuologia Clinica di Roma. *Rivista di Sessuologia Clinica, 98, (2),* 7-14.

Rotter, J. B. (1966). Generalized expectancies for internal versus external control of reinforcement. *Psychological Monographs, 80,* 609.

Salovey, P., and Birnbaum, D. (1989). Influence of mood on health-relevant cognitions. *Journal of Personality and Social Psychology, 57,* 539-551.

Savin-Williams, R., and Diamond, L. (2004). Sex. In R. M. Lerner, and L. D. Steinberg (Eds.)*Handbook of adolescent psychology* (pp. 189−231). Wiley.

Simonelli C., and, Fabrizi A. (1996). Vaginismo e dispareunia. In C. Simonelli (Ed.) *Diagnosi e trattamento delle disfunzioni sessuali*. Milano: Franco Angeli.

Simonelli C, Fabrizi A, Napoli M. (2001), "Il vaginismo: rassegna della letteratura", Rivista di Sessuologia Clinica, 2: 87-99.

Simonelli C. (2002). *Diagnosi e trattamento delle disfunzioni sessuali.* Milano: Franco Angeli.

Simonelli C., Rossi R. (2003), "Componenti psico-sessuologiche nel nostro contesto culturale" in Cioffi L., De Placido G., Fusco F., Mirone V., Montorsi F., Nappi R. E., Calmieri A., Pirozzi Farina F., Rellini A., Salonia A., Simonelli C., "Le disfunzioni sessuali femminili", pp. 81-88, Pacini Editore, Pisa.

Simonelli C, Fabrizi A., Vizzari V., Accattatis C. (2004), "Le disfunzioni sessuali femminili nell'esperienza di un centro clinico di sessuologia", Andrologia 2004, atti del XXI Congresso Nazionale delle Sezione Regionali SIA, Roma, CIC edizioni internazionali: 93-97.

Simonelli C. (Ed.) (2006). *L'approccio integrato in sessuologia clinica*. Milano: Franco Angeli.

Simonelli, C., Fabrizi, A., Rossi, R., Silvaggi, C., Tripodi, F., and, Michetti, P.M. (2010). Clinical sexology: An integrated approach between the psychosomatic and the somatopsychic. *Sexologies, 19 (1),* 3-7.

Stief, C.G., and, Hartmann, U. (2003). Procedimento pratico e valutazione critica. In C.G. Stief, U. Hartmann, M.C. and U. Jonas, *Terapia della disfunzione erettile*. Roma:CIC.

Symons, D. (1995). Beauty is in the adaptations of the beholder: The evolutionary psychology of human female sexual attractiveness. In P.R. Abramson and S.D. Pinkerton (Eds.) *Sexual Nalure/Sexual Culture* (pp. 80-118). Chicago: University of Chicago Press.

Smith, C.A., Griner, L.A., Kirby, L.D., and Scott, M.S. (1996). Toward a process model of appraisal. In N.H. Frijda (Ed.), *Proceedings of the IXth Conference of the International Society for Rsearch on Emotions,* Toronto, 101-105.

Strickland, B.R. (1988). Internal-external expectancies and health-related behaviors. *Journal of Consulting and Clinical Psychology, 46,* 1192-1211.

Veglia F. (2000). *Handicap e sessualità: il silenzio, la voce, la carezza*. Franco Angeli: Milano.

World Health Organization (n.d.). Gender and reproductive rights. Retrieved March 10, 2010, from http://www.who.int/reproductivehealth/en/.

Zucker, K. J., and Bradley, S. J. (1995). *Gender identity disorder and psychosexual problems in children and adolescents.* New York: The Guilford Press.

In: Male Sexual Dysfunctions in Neurological Diseases… ISBN 978-1-61761-855-0
Editor: Calabrò Rocco Salvatore

Chapter 3

Clinical and Instrumental Diagnosis of Sexual Disorders

Giuseppe Gervasi, Placido Bramanti, Paolo Di Bella, Nunzio Muscarà, Silvia Marino and Rocco Salvatore Calabrò

Abstract

The recent identification of the elements of sexual response and the understanding of their functioning have given a support in investigating patients with sexual disorders. Indeed, the different psychological, vascular and local genital changes have to take into account while exploring every single sexual function. Then, Walsh's classification of sexual cycle into 5 specific sequences (i.e. libido, erection, ejaculation, orgasm, and detumescence) is useful in clinical practice to better assess the specific sexual impairment of complained patients. Around 2005 and 2006 the American urological Association and the European Association of Urology have drawn the guidelines for the management of erectile dysfunction. Specific guidelines to explore sexuality in neurologic patients are lacking with the exception of those built in 2001 by the European Federation of Neurological Society. In our opinion, a complete investigation on sexual problems in neurological patient could improve quality of life in these patients, especially when young. A complete evaluation of sexual function should include an accurate anamnesis with a proper neurological and physical examination, followed by a specific instrumental investigation exploring the vascular, hormonal, neurological and urogenital components of sexual response. Herein, we promote a specific flow-chart with a differentiation into three different analysis-levels.

Introduction

Significant advances in understanding the physiology and pathophysiology of male sexual function have been attained during the last decades. In the field of physiology, the nature and elements of the normal sexual response have been delineated, and functional

activities of all penile structures have been clarified. The exact role of the various components of the neural system has also become more fully understood. In the field of pathophysiology, estimations of the specific contribution of psychogenic and organic factors to the genesis of the various forms of male sexual dysfunction have approached reality. In the field of physical and laboratory evaluation, many new psychometric, hormonal, vascular, and neurological investigative procedures have been attempted. As a result, sound techniques for accurate prediction of functional and structural changes are now emerging [1].

In the previous chapters, the anatomo-physiology of male sexual function has been highlighted, and the psychological control of the human sexuality has been mentioned. The aim of this chapter is to pay attention to the clinical presentation of male sexual dysfunctions and the instrumental evaluations that are useful to diagnose them.

Anatomo-Physiology of Male Sexual Function

The penis is composed of two functional compartments: the paired corpora cavernosa and the corpus spongiosum. Interspersed within this parenchyma, there is a complex network of endothelial cell-lined sinuses (also called lacunae) and helicine arteries. These arteries and the lacunae supply a correct blood flow throughout corpora cavernosa and corpus spongiosum that are useful to the erection [2].

The penis is innerved by somatic and autonomic nerve fibers. The somatic innervation provides the sensory fiber for the penis. The autonomic innervation is both sympathetic and parasympathetic. The sympathetic innervation of the penis mediates the detumescence after the orgasmic relief, and, in the absence of sexual arousal, it maintains the penis in flaccid state. The parasympathetic pathway originates in the intermedio-lateral aspect of the sacral cords (S2-S4) travelling in the pelvic nerve to supply a vasodilating innervation to the corporeal bodies. The sacral parasympathetic neurons are influenced by a cortical-sacral efferent pathway [3].

Sexual stimulation of the human male results in a series of psychological, neuronal, vascular and local genital changes. In the previous years many classifications for these changes have been described. In 1987, Walsh focused the classification on the functional activities during the sexual cycle. Thus, the normal male sexual response cycle can be functionally divided into five interrelated events that occur in a defined sequence:

- *Libido or sexual desire*, the biological need for sexual activity, frequently expressed as sex-seeking behavior.
- *Erection*, the ultimate response to multiple psychogenic and sensory stimuli from imaginative, visual, auditory, olfactory, gustatory, tactile, and genital reflexogenic sources, which effects several neurological and vascular cascades that lead to penile tumescence and rigidity sufficient for vaginal penetration.
- *Ejaculation*, the result of a spinal cord reflex arc controlled by autonomic innervation of the genital organs; this phase is strictly related with the previous one.
- *Orgasm*, a sensory cortical perception of pleasure determined by both physiological and psychological elements during sexual intercourse.

- *Detumescence*, the last phase in which the penis returns to the flaccid state with a blood flow rate similar to the pretumescence level, and followed by a period of inhibition to resumption of erection and ejaculatory function (depending on age, physical state and psychological environment).

According to this classification, a preponderance of psychological control in the libido phase can be noted, followed by a predominance of neurological control in the erection, ejaculation and detumescence phases; only in the orgasmic phase there is a balance between neuronal and psychological control. The erection phase is also mediated by a local control, mainly due to the vasodilating effect of Nitric Oxide (NO). NO is synthesized from its precursor, L-arginine, by the enzyme nitric oxide synthase (NOS). Both constitutive and inducible NOS isoforms are produced in the endothelial cells of the cavernosal tissue [1, 4, 5].

Male Sexual Dysfunction

Identification of the sexual response components involved in sexual dysfunction can significantly reduce the number of investigations required to identify the underlying etiologies. However, the exact contribution of each etiological category to the genesis of a given dysfunction may be difficult to establish, but the knowledge of its characterization is essential for treatment planning. For these reason, physicians should consider the context in which the sexual symptom develops, analyzing the partner's relationship, behaviour and diseases.

Male sexual dysfunctions could be classified into three classes: disorders of sexual function, disorders of sexual orientation, and disorders of sexual behavior. The disorders of sexual orientation and sexual behavior are believed to be entirely due to psychological etiologies. Thus, for the assessment of these disorders it is possible to refer to the Diagnostic and Statistical Manual of Mental Disorders – IV (DSM-IV) and to the International Classification of Disease – 10 (ICD-10) [1,6,7].

In 1993 the National Institutes of Health Consensus Development Conference (8) advocated that "erectile dysfunction" must be used instead of impotence to describe disorders of male sexual function and defined the new terminology as the "inability to achieve an erect penis as part of the overall multifaceted process of male sexual function". However, the use of the term "erectile dysfunction" to refer to all the aspects of male sexual function would be inappropriate.

To better assess the clinical manifestation of every single male sexual dysfunctions, we will analyze them according to Walsh's classification [1].

Disorders of Desire

The disorder of desire is less frequent in male rather than female and usually increases with age. Sexual desire or arousal consists of the mind's processing of internal sexual stimuli and external stimuli and their context. It is the first phase of the normal sexual response that predisposes complex brain circuitries involving those cortical, limbic and paralimbic regions known to be associated with cognition, emotion and motivation. These circuitries mediate the

right sex-seeking behaviors and modulate the autonomic nervous system of lumbosacral regulating erection and ejaculation phase. Therefore, many psychological, neurological and local factors could determine an altered sexual desire [9].

Pathologically the disorders of desire can be distinguished into an increasing or a reduced sexual desire, and in an altered sex-seeking behavior.

The most common disorder of desire is by far the *Hypoactive Sexual Desire* (HSD) also called hyposexuality, that is defined as a persistently or recurrently deficient (or absent) sexual fantasy and desire for sexual activity leading to marked distress or interpersonal difficulty.

The diagnosis of primary desire loss in men can only be made after eliminating the presence of factors known to affect the sexual function. Thus major psychiatric disorders, chronic medical conditions, intake of pharmacological agents, or substance abuse have to be excluded.

Disorders of sexual desire are mainly caused by psychogenic factors and androgen deficiency. Psychogenic conditions leading to a desire deficiency state in men include psychiatric illness such as depression or psychosis, preoccupation with life crisis or grief, gender identity conflicts and aging-related psychological issues [1,10,11].

A particular form of psychogenic desire disorder is termed “excitement inhibition”. It is commonly seen in patients who have sexual drive but cannot maintain excitement with performance anxiety due to the fear of sexual failure and the vigilant preoccupation with erection during lovemaking [12,13].

The other common form of HSD is due to a low blood androgens concentration. A critical level of blood androgens is required for the maintenance of normal sexual desire, even if it is still a controversial debate. Nevertheless, in hypogonadic state there is some evidence of HSD, but the concentration of testosterone required for maintaining libido is lower than for supporting spermatogenesis and growth and function of prostate and seminal vesicles [18].

Also patients with a CNS disease such as Epilepsy, Parkinsonism, Stroke and Adrenoleukodystrophy may have a diminished sexual arousal. The pathogenesis of loss of desire in these neurological disorders appears to be multifactorial in origin and includes disease-related hormone abnormalities, physical restrictions and reduced well-being [14-17].

Finally, several pharmacological agents (mainly antihypertensive and psychiatric medications) or substances of abuse could potentially induce hyposexuality through different mechanisms of action which will be better explained elsewhere [1,19,20].

Hypersexuality, also called compulsive sexual behavior, is characterized by inappropriate or excessive sexual cognition or behavior that lead to subjective distress or impaired functioning in one or more important life domains. Psychiatric illnesses are considered to be the most frequent cause of abnormal sexual behavior, but many neurological disorders can interfere with a right sexual behavior especially the degenerative ones such as Parkinson, Alzheimer diseases [1].

Erectile Dysfunction

The National Institutes of Health (NIH) Consensus Development Conference on Impotence defined ED as “the inability to achieve or maintain an erection sufficient for satisfactory sexual performance” [21].

Erectile function is a haemodynamic phenomenon depending on the integrity of neurological, vascular, endocrinological, tissutal (corpora cavernosa), psychological and relational factors; changes in any one of these components may lead to ED. Clinically ED appears as a difficulty to have or keep a proper erection and tumescence of the penis. Evaluation and characterization of all factors underlying ED is essential for a correct diagnosis and a good therapeutic approach [22,23].

ED and its comorbid conditions share common vascular risk factors such as endothelial dysfunction, atherosclerosis and metabolic and hormonal abnormalities. Although cross-sectional studies have shown a clear age-dependent association between ED, diabetes mellitus, hypertension, metabolic syndrome, and cardiovascular disease, longitudinal evidences have recently emphasized that ED could be an early marker of these conditions. Hence, ED can be considered the starting point for the evaluation and prevention of these significant severe diseases hitherto unknown by the patient [19,24-29].

Although aging is associated with different morbidities which could interfere with endothelial function, it has been demonstrated that age is an independent risk factor for ED [30,31]. Nicolosi showed a significant association between ED and age in a healthy male population free from comorbidities, such as cardiovascular and prostate disease, diabetes, and depression [32]. Schiavi and Rehman hypothesized that the threshold for the biological action of testosterone might be higher in elderly men compared to young men [33]. This hypothesis was confirmed by Isidori and Gray that showed how in elderly men libido and erectile function responded only to higher levels of circulating testosterone than in younger men [34, 35].

Circulating levels of testosterone are necessary to maintain the integrity of the anatomical structures of the penile erectile tissue. Furthermore, beyond the well-known role of testosterone in regulating NO formation, Morelli demonstrated, for the first time, that testosterone also regulates the expression of PDE5 gene and enzyme activity in human corpus cavernosum [36]. The main physiological action of testosterone is therefore to timely adjust the erectile process as a function of sexual desire and to finalize erection with sex [37,38].

As we have mentioned previously, many severe and chronic diseases (i.e. diabetes mellitus, metabolic syndrome and cardiovascular disease) are related to ED.

Among men with diabetes mellitus, the prevalence of ED is significantly correlated to the duration of the disease, glycometabolic control and presence of comorbidities. Diabetes Mellitus-related ED is thought to be multifactorial in aetiology and to include vascular (microangiopathy) and neurological (polyneuropathy) factors [39-41]. A large clinical trial has demonstrated that prevalent or incidental ED predicted the occurrence of cardiovascular events over a follow-up period of 9 years. ED may represent the early clinical evidence of a diffuse vascular damage in men with different vascular risk factors but no other evidence of atherosclerosis. Therefore, incidental ED predicted subsequent acute coronary artery disease to a degree equal or greater than any other vascular risk factors; especially in diabetes mellitus, ED was the most efficient predictor of angiografically verified silent cardiovascular disease. The pathogenesis of an early development of ED in subjects with many vascular risk factors may reside in the impairment NO release from endothelial cells upon neuronal activation of penile erection [24,42-44].

Moreover a very complex relationship between diabetes, metabolic syndrome, cardiovascular diseases and ED can be found out. The most important aspect of this hypothesis is the characteristic metabolic changes of the patients with central and abdominal

obesity. Abdominal obesity can lead to endocrinological imbalances with an increase in insulin, glucose and C-peptide levels, and a decrease in testosterone levels. A possible mechanism that may account for this inverse relationship involves elevated serum leptin levels in individuals with large fat reserves. Indeed, elevated leptin levels interfere with luteinizing hormone (LH)/human chorionic gonadotrophin stimulated androgen production ratio suppressing androgenic hormone formation. Decreased sex-hormone binding globulin, increased aromatization of testosterone to estradiol in fat cell or cytokine-mediated inhibition of testicular steroid production are other possible pathogenetic mechanisms to take into account. Therefore, men with abdominal obesity are in a vicious cycle as testosterone deficiency leads to reduced lipolysis, reduced metabolic rate, visceral fat deposition and insulin resistance [45-47].

Other common causes of ED are prostate diseases, psychorelational factors and neurological diseases.

The Multinational Survey of Aging Male clearly demonstrated that Lower Urinary Tract Symptoms (LUTS) are an independent risk factor for sexual dysfunction in older men [48]. Indeed, an association linking a reduced maximal urinary flow rate, increased prostate volume and ED severity has been reported. The pathophysiology of sexual dysfunction in men with severe lower urinary tract diseases is not clearly understood. An increasing sympathetic and adrenergic tone, as well as the reduced quality of life of patients with an increasing anxiety and a loss of sexual interest could play an important role in the pathogenesis. Finally, antiandrogen drugs and surgery used in the treatment of these urinary diseases could determine ED [49,50].

The aetiology of ED is traditionally thought to be either organic or psychogenic, in a dichotomized view which is, indeed, far from reality. When a sexual encounter results in frustration and stress rather than gratification, it is possible to construct a vicious psychoneuroendocryne cycle of distress and depression early developing in ED [23,26,51].

ED can be due to any lesion affecting the central and peripheral nervous system. Peripheral ED can be secondary to the disruption of sensory nerves that bring local information to the brain, or to the disruption of autonomic nerves which mediate arterial dilatation and trabecular smooth muscle relaxation. Central origin of ED can occur in case of lack of excitation as well as in case of an increasing inhibition of central autonomic pathways [52]. The most important cause of ED is spinal cord injury, whereas the outcome depends on the location of the lesion. In upper motor neuron lesions 95% of men are capable of reflexogenic erection, while in lower motor neuron lesions only 25% of men can achieve psychogenic erection. Moreover, more than 90% of patients with an incomplete lesion retain erectile function. Injury to cavernosal nerve may also lead to ED since it is present in about 80% of the patients treated with surgery or beam radiation therapy for prostate cancer [53-55].

Disorders of Ejaculation

Disorder of ejaculation is a common sexual dysfunction among young men. The ejaculatory process is mediated by the autonomic nervous system and consists in two different phases: emission and expulsion. During the emission phase, spermatozoa are ejected into the posterior urethra and mixed with products secreted by accessory sexual glands, i.e.

prostate and seminal vesicles. The process is mediated by sequential epithelial secretion and smooth muscle cell contraction. The expulsion phase is characterized by the ejection of the semen from the urethra through the glans meatus. This phase is determined by the rhythmic contraction of pelvic floor muscle, such as bulbospongiosus and ischiocavernous muscle. Beside this mechanism, the smooth muscle fibers of the bladder neck contract to prevent the backward flow of the semen into the bladder. During this process, the external urinary sphincter is relaxed. The organs involved in the ejaculation phases have a dense sympathetic (noradrenergic) and parasympathetic (acetylcholinergic) innervation mainly derived from the pelvic plexus and dorso-lumbar spinal cord centers. Furthermore the spinal cord generator of ejaculation is under the inhibitory and excitatory influences of supraspinal sites, i.e. nucleus paragigantocellularis, paraventricular nucleus of hypothalamus and the medial preoptic area.

The most common cause of ejaculation disorder is considered by far a psychogenic factor that can modulate the length of duration. There exists a spectrum of these disorders ranging from mild premature to severely delayed or absent ejaculation. Normally, the right ability to control ejaculation is acquired by about age 17 or 18. In this spectrum of diseases, the most reported dysfunction is *Premature Ejaculation* (PrE).

The DSM-IV defines the diagnostic criteria for PrE as follows:

A. Persistent or recurrent ejaculation with minimum sexual stimulation that occurs before, upon, or shortly after vaginal penetration and before the person wishes it;
B. Marked distress or interpersonal difficulty;
C. Condition does not arise as a direct effect of substance abuse, i.e. opiate withdrawal.

PrE is the most frequent reported problem in young adult male [56,57]. The causes of PrE can be divided into psychorelational, neurobiological, urological, hormonal and androgenical. Among the most common psychorelational factors there are anxiety, adverse familial and partner relationship, religious beliefs and false convictions about sexuality. Beside this theory, many studies have shown a neurobiological phenomenon due to chronic central serotoninergic hypoactivity. Serotonin pathways seem to act a primary role at several levels in the neuraxis. According to the principle findings of several experimental and clinical models, the overall effect of serotonin on ejaculation is inhibitory.

Local aetiologies of PrE include short frenulum, prostatic inflammation, and a penile hypersensitivity and reflex hyperecitability, although many authors have not shown a correlation between the penile sensitivity and the ejaculation latency time. Sometimes PrE shares a vicious cycle with ED, in which a man trying to control his ejaculation instinctively reduces his levels of excitation. Recently, hyperthyroidism has been shown to be a possible predisposing factor to PrE. The relationship between thyroid hormone and ejaculatory dysfunction is currently unknown.

Diagnosis of PrE is straightforward, simply based on patient self-report, clinical history, sexual history and examination findings. The main objective is to quantify the length of time between penetration and ejaculation. A multidimensional assessment of patients affected by PrE, including psychosocial involvement, is also needed. One of the most widely-used questionnaires is the Premature Ejaculation Diagnostic Tools.

Retrograde Ejaculation is defined as the backward flows of the semen into the bladder. All the components of the ejaculatory reflex are present, except for bladder neck closure. The

patient might notice cloudy postorgasmic urine for the presence of the semen. The most common cause is the surgical disruption of the genital autonomic nerve supply after prostatectomy. Because seminal emission and bladder neck closure are both controlled by alpha-adrenergic neurons, all the medical conditions (e.g. spinal cord injury) and specific drugs (e.g. antihypertensives, neuroleptics and antidepressants) altering adrenergic pathways might cause the retrograde ejaculation. Diagnosis could be made by taking an accurate history of previous surgical procedures and drugs consumption. Then, retrograde ejaculation can be confirmed by demonstrating sperm presence in the post-coital urine [58,59].

Painful Ejaculation (PE) is commonly reported as a persistent and a recurrent pain in the genital organs during ejaculation or immediately afterward. The most common cause of PE is a psychogenic factor, although in some cases it is possible to point out an organic aetiology. In a few cases, it has been reported as a side effect of tricyclic antidepressant drugs [1,60,61].

In his studies Barnas reported that 50 to 80% of normal subjects experienced pain for 1 to 5 minutes after orgasm [62,63]. The presence of pain starting after ejaculation and lasting over 2 hours could lead to the diagnosis of PE. Pain varied from minor discomfort to disabling pain, with possible avoidance of intercourses for months. When PE is due to a local aetiology, the cause may vary depending on age, but it is often assessed as a symptom of the LUTS, especially when a Chronic Pelvic Pain Syndrome exists. In young people PE is most commonly due to an ejaculatory duct stone or a traumatic pudendal neuropathy caused by a repetitive action (i.e. sitting, repetitive climbing, and flexion exercises of the hips). Many authors have described the sites of the trauma: Robert et al [64] evidenced the compression between sacrotuberous and sacrospinous ligaments, impingement at the falciform process of the sacrotuberous ligament, or compression of the pudendal nerve as it traverses the pudendal (Alcock) canal; Myers [65] described the role of the obturator internus muscle as a pelvic thruster; Shafik [66] highlighted microanatomical structures that facilitates gliding of the pudendal nerve between the layers of obturator fascia during hip flexion. In all aforementioned conditions, pelvic movements during intercourse might be considered as the pathophysiological cause of the pain. In the elderly PE is often referred in patients after prostatectomy or beam radiation therapy for prostate cancer. In these subjects the physiological bladder neck closure that occurs during orgasm translates into spasm of the vescico-urethral anastomosis, or dystonia of the pelvic floor muscles [63,67].

Iatrogenic PE is commonly associated to antidepressant medication. Ferguson [68] described the highest rates of sexual dysfunction with antidepressants acting primarily on serotoninergic system including selective serotonin reuptake inhibitors (SSRI), tryciclic antidepressants such as clomipramine, and serotonine/noradrenaline reuptake inhibitors (SNRI) such as venlafaxine. Since the expulsion phase of ejaculation is mediated by the adrenergic system (α1-R), also the α1-R antagonist can lead to ejaculatory dysfunctions [69-70].

Disorders of Orgasm

DSM-IV (6) and ICD-10 [7] defined the disorder of orgasm as a persistent or recurrent delay or absence of orgasm after a normal sexual excitement phase during sexual activity and not better accounted by other medical disorders, substance abuse or general medical condition. This disorder is more often frequent in female than in male. In the Global Study of

Sexual Attitudes and Behaviours [30], a prevalence of 5 to 17% of difficulties of reaching orgasm in man between 40 and 49 years was reported.

Orgasm in men is often entwined with ejaculation: it starts from the prostate contraction and continues throughout semen ejection. During orgasm, people experience some pleasure sensation that resolves in sexual satisfaction. For this reason disorder of orgasm is often presented and disguised with disorders of ejaculation. Both the terms anorgasmia and anejaculation are used to refer to the same disorder.

Orgasm and sexual satisfaction are often determined by psychological conditions, i.e. relationship with partner, subjective health, socially compatible personality and lack of physical complaints. Thus, personal history is often crucial in reaching diagnosis.

The term "idiopathic" anorgasmia is used to indicate a condition when there are no demonstrable neurologic derangements to orgasm dysfunction. Several reports link inability to achieve orgasm in otherwise healthy individuals to other psychogenic issues, such as anxiety. Since some subjects are able to reach orgasm and ejaculate with masturbation but not during sexual intercourse, and since they can present nocturnal emission, a psychogenic origin is suggested.

Sometimes orgasm dysfunction is related to frequent masturbations or use of idiosyncratic masturbation techniques. Changing the stimulation technique and decreasing the frequency of masturbation have been successful in reversing the problem [59].

At the same time, most of the degenerative CNS diseases (such as Multiple Sclerosis, Parkinson's disease, Huntington's Corea), or some drugs acting on CNS (such as SSRI, I-MAO, tryciclic antidepressant), or the abuse of substances of addiction may produce disorder of orgasm. The pathophysiology of these neurological causes is mostly based on the altered somatosensory control, that can reduce the pleasure sensation, or on a dysregulation of the sympathetic autonomic system, that can demodulate the final ejaculation phase [1].

Disorders of Detumescence

The disorders of detumescence may be divided into two categories: prolonged refractory period and failure of detumescence.

The latter is the most common and it is also known as Priapism. A clinical characteristic of Prisapism is a prolonged and extremely painful erection unaccompanied by sexual desire and often preceded by sexual stimuli. Priapism is usually divided into an idiopathic and a secondary form.

According to some investigators, the idiopathic form constitutes as much as half of all registered cases and it has long been recognized as priapism without a discernable clinical cause. This form has been associated with sporadic previous priapism episodes and particularly with erection that is sustained for prolonged duration of sexual activity [72,73].

The secondary form can be due to several causes. It can be observed in abnormality of penile blood flow, in abnormality of erectile neuroregulation and in altered regulatory mechanism of erectile tissue.

The physiopathology of priapism is different in each of these conditions. According to the abnormal penile blood flow, we can distinguish a low-flow and a high-flow priapism. The former, also called ischemic priapism, seems to be related to an impairment of the veno-occlusive mechanism: all the diseases concerning an increased intravascular viscosity (i.e.

sickle cell disease, parenteral alimentation with fat emulsion, hemodialysis, hematological dyscrasis) or an increased blood coagulability (i.e. intracavernosal heparin administration) or the presence of venous infiltration or obstruction (i.e. local tumor or neoplastic process) could determine a low-flow priapism. The latter is mainly due to an abnormal arterial overflow in penile vessels. The most common cause of this disease is a local trauma often complicated by the formation of a fistula between the arterial inflow vessels and the venous and sinusoidal outflow circulation of the penis [74,75].

When priapism is due to an abnormal erectile neuroregulation, several mechanisms have been proposed to explain the role of neurological disease in the pathogenesis. Indeed many diseases (i.e. infections, brain tumors, epilepsy, intoxication, brain and spinal cord injury) can directly affect the erectile center and its connections leading to the failure of the autonomic sympathetic nervous system that could readily predispose to the development of priapism [72,76].

An altered regulatory mechanism of erectile tissue at the origin of priapism can be postulated on the observation that many regulatory factors influencing the functional state of the cavernosal tissue can work somehow in a dysfunctional manner, and can be activated under those pathological conditions affecting erectile physiology. Several plausible mechanisms may contribute to the physiopathology of priapism: from a physiologic increase in oxygen tension within the cavernosal tissue, to an aberrant nitric oxide regulation, to an altered contraction of the smooth muscle cells. This dysregulatory mechanism may be associated with idiopathic priapism or other divergent presentation of priapism (i.e. stuttering, refractory, drug-induced priapism), well distinguished from the classic haemodynamic types of priapism [77].

The prolonged refractory period is almost always seen in elderly people and it is mainly due to all those diseases that can determine a dysregulation in the normal tissue erection (i.e. sensory polyneuropathy, diabetes mellitus, etc).

Diagnostic Assessment of Male Sexual Disorders

Recent findings have shown that sexual activity and desire are common also among middle-aged and elderly people and persist into old age worldwide. Sexual activity is essential for self-esteem and to maintain a proper relationship. Nevertheless, Nicolosi et al. have noticed that the prevalence of sexual dysfunction is quite high and increases with age [30].

Sexual dysfunction is an emerging problem and, nowadays, more subjects tend to refer to their physician, because they are also heartened by the new oral therapy for ED. In this chapter we paid attention to the American Urological Association (AUA) and the European Association of Urology (EAU) guidelines that focused their attention on the management of ED, and to the European Federation of Neurological Societies guidelines [78-80]. This Task Force on Neurosexology observed that sexual symptoms and problems of patients with neurological disorders are often poorly described and can hence be often misinterpreted, so after some hard work, proposed specific guidelines for neurologists.

In our opinion, diagnostic assessment of sexual disorders in male patients consists of three phases: anamnesis, physical examination and instrumental investigation.

Anamnesis

Anamnesis is the key element of clinical approach. It enables the identification of risk factors, in order to look into either the organic or psychological pathogenesis of the sexual dysfunction, and acts as a guide for further diagnostic evaluation.

From a general point of view a patient's personal history should include a survey of his medical history in order to define the medical condition predisposing to sexual dysfunction. This must be followed by a detailed history related to the sexual dysfunction so defining the patient's sexual expectations, needs and behavior as well as identifying sexual problems and misconceptions. This step is important to clarify the nature and the characteristics of sexual dysfunction, to discover an underlying organic cause and to document the existence of primary or secondary psychological factors.

In the assessment of patients with sexual dysfunction, a quantification scale to standardize the gravity of the symptoms as well as to provide objective measurement of specific treatment may be useful. The most used questionnaires are by far the Brief Male Sexual Function Inventory for Urology [81] and the International Index of Erectile Function (IIEF) [82]. The main limitation of these questionnaires lies in their nature, since patients fill them in without any assistance from the physicians. So, the patient may misinterpret the questions and it is difficult for him to knowingly choose the most suitable answer. Moreover, the questionnaires can interfere with the patient-doctor relationship which is essential part for the diagnosis. As a matter of fact, it has been suggested that these texts are helpful in studies concerning treatment efficacy but not in everyday practice [83].

The anamnesis should be divided into three specific parts to better investigate the different aspects of sexual function: medical, sexual and psychosocial anamnesis.

Medical anamnesis investigates the healthy component of sexual dysfunction. The family history is useful to establish the patient predisposition for the development of diabetes, endocrine and cardiovascular diseases. The personal history is useful to allow the identification of risk factors or those conditions predisposing to sexual dysfunctions. The patient should be asked about its habits as regards smoking, alcohol consumption, drugs abuse, sleep-wake cycle, physical exercise, food intake, kind of job, and also about defecation and micturition. The pathological anamnesis should help to assess any chronic concomitant disorders in particular cardiovascular diseases which can determine sexual dysfunction. Moreover, iatrogenic ED has to be taken into account when counseling patient (table 1)

Sexual anamnesis focuses on the reason that leads patients to their doctor. First, it is important to evaluate the exact kind of problem at hand, the time of onset of dysfunction and how it became manifest. This is particularly important in neurological patients presenting sexual dysfunction. Patients must be carefully questioned about sexual desire and stimuli, erection, ejaculation, orgasm and detumescence. The chronology is very important: a sudden onset in the absence of any organic pathology tends to a psychological origin; a gradual and progressive onset of the disorders leads to the organic form.

Table 1. Drugs associated with ED

INCIDENCE	CLASS	INDIVIDUAL AGENTS
Frequent	Antihypertensives	Thiazides diuretics
		Spironolactone
		Aldosterone blockers
		α-methyldopa
		Clonidine
		Reserpine
		β-blockers
		Guanethidine
		Verapamil
	Psychotropic	Phenothiazines
		Butyrrophenones
		Benzamides
		Pimozides
	Antidepressants	Tricyclic
		IMAOs
		SSRI
		Lithium
	Prokinetics	Metoclopramide
		Domperidone
	Antiepileptics	Barbituates
		Carbamazepine
	Cardiotoinc	Digitalis
	Hypolipemic – Hypocholesterolemic	Fibrates
	Hormones	Estrogens/progesterone
		Corticosteroids
		Cyproterone acetate
		5-α reductase inhibitors
		LHRH agonists
Low	Antihypertensives	A-blockers
		ACE inhibitors
		Calcium antagonist
	Antiepileptics	Phenitoin
		Valproic acid
		Lamotrigine *(Absent)*
	Antianginal	Nitrate
		Hydralazine
	Antihystaminergic H2	Cimetidine
		Ranitidine

So it is important to consider how the problem has evolved during the time and its impact on the couple relationship. Thus, sexual anamnesis should be conducted not only with the patient alone but also with his partner. Moreover, it is important to know the health status and sexuality of the habitual partner and investigate any possible couple-relationship problems. It is also important to find out whether the patients enjoy or practice sex outside the couple and so whether or not the sexual problem is present in other relationships.

Psychosocial anamnesis enables the identification of psychological or relational situations which might negatively influence sexual activity. Tiefer and Schuetz-Mueller have

considered these psychosocial factors distinguishing them into predisposing, precipitating and maintaining conditions (*see Table 2*). Psychological issues have already been discussed in the previous chapter [43,78-80].

Table 2. Psychopathological causes of ED

Predisposing	Precipitating	Maintaining
• Lack of sexual knowledge • Poor past sexual experience • Relationship problems • Religious and cultural beliefs • Restrictive upbringing • Unclear sexual or gender preferences • Previous sexual abuse • Physical or mental health problems • Other sexual problems in the man or his partner • Drugs	• New relationship • Acute relationship problems • Family or social pressure • Pregnancy and childbirth • Other major life events • Partner's menopause • Lack of knowledge about normal changes of ageing • Acute physical or mental health problems • Other sexual problems in the man or his partner • Drugs	• Relationship problems • Poor communication between partners • Lack of knowledge about treatment options • Ongoing physical or mental health problems • Other sexual problems in the man or his partner • Drugs

Physical Examination

Physical examination is carried out in order to confirm what has emerged from the interview, as well as what the patient does not state or expresses in a confused manner due to emotion or reticence.

The physical examination of a patient affected by sexual dysfunction needs to consider a general evaluation followed by a specific examination of the single component of the sexual function, mainly focused on cardiovascular, gonadal and neurological system.

In the general evaluation body parameters (muscle mass, fat distribution, body weight, body mass index) clinical signs of concomitant diseases (i.e. neoplasm, hepatic and renal disease and endocrine) or their complications such as gynecomastia absence or altered hair distribution, cutaneous abnormalities and dyschromias should be evaluated.

Cardiovascular examination should include a careful cardiac examination, a quantification of the blood pressure, an evaluation of the pulses and vascular murmurs especially in the lower limbs.

Gonadal examination must focus on penis, testicles and glands. With regard to the penis it is important to determine dimension and form in a state of flaccidity, the examination of the

corpora cavernosa to evidence the possible presence of malformation or specific disease (such as fibrosis, atherosclerotic plaques) that could interfere with a right erection, the flow of the praeputium upon the glans, location and patency of the urethral meatus. The examination of testicles evaluates morphology, consistency and pain in the testicle region, and the presence of a possible pampiniform plexus ectasia (i.e. varicocele). Finally the glands examination is mainly focused on the prostate evaluation by rectal exploration. It is very important to determine morphology, volume, consistency and pain in the elderly , and to confirm the presence of a possible hypogonadism in young people [43].

The standard neurological examination, including assessment of mental state, should reveal any possible signs of the underlying neurological disease that could interfere with normal sexual response. The sacral segments are of particular interest. Beside the standard examination, tactile and vibratory sensitivity in the genital area and bulbocavernosus muscle with their voluntary and reflex contraction should be evaluated. Therefore, in addition to the standard reflexes, cremasteric, bulbocavernosus and external anal reflexes that investigate autonomic pathways involved in sexual function have to be tested. The cremasteric is a somatosomatic reflex testing the L1 segment; it is elicited by lightly stroking the superior and medial (inner) part of the thigh with a consequent contraction of cremasteric muscles that pulls up the scrotum and testis on the stroked side. This reflex helps to investigate the integrity of the lumbar centre where the sympathetic pathways involved in the coordination of sexual function (mainly mediating detumescence) are located. Otherwise, the bulbocavernosus and external anal reflexes test the S2-S4 segment involved in the parasympathetic pathways. The bulbocavernosus is another somatosomatic reflex that is elicited by squeezing the glans and observing contraction of anal sphincter or, but only in male, assessing the contraction of the bulbocavernosus muscle by palpation. The external anal reflex, instead, is useful to test the touch and pain perception in the perineum, perianal and genital skin; it is elicited by repetitive pricking or scratching the perianal skin and observing the anal sphincter contraction [80,84].

Instrumental Investigation

The instrumental investigation is built up to confirm the suspicion made by history and physical examination and, typically, used to evaluate erectile function and capacity since the other aspects of normal male sexual response are better assessed by a psychological approach and better diagnosed using DSM-IV and ICD-10.

As we have previously mentioned, every single component of male sexual response might be caused by many organic factors. Then, it is possible to ensure a diagnosis of a psychological/psychiatric genesis of sexual dysfunction if and only if all the instrumental evaluations did not make evidence of any urological, neurological, hemodynamic, metabolic or iatrogenic disease producing sexual disorders.

The AUA and EAU guidelines focused their attention on the management of therapy in patients suffering of ED with urological disease. As sexuality can be altered also by neurological diseases, neurologists have to know how to manage neurological patients with sexual dysfunction. To our knowledge, since 2001 only the Task Force on Neurosexology of the EFNS has given guidelines for the management of sexual dysfunction in neurological patients.

As the lack of new specific guidelines may cause some trouble in the clinical approach to these patients, we suggest the use of a flow chart for a right diagnosis as explained in Figure 1.

First of all, we can distinguish three different levels of instrumental approach to sexual dysfunction, as the choice of investigations depends on the clinical conditions of the patients:

- First level: at this level we can find all the tests that could aim to determine possible causes and concomitant underlying systemic diseases, since sexual disturbances may represent the first symptoms. These are mainly non-invasive or less invasive diagnostic tools.
- Second level: at this level we group some diagnostic tools that are specific and useful to diagnose sexual dysfunction, because they can better explain the erectile function. These are specific and expensive tests that are also difficult to perform; so they should be carried out in highly specialized centers only.
- Third level: in this level it is possible to find all those techniques that are not useful for the diagnosis, but could refine or give more information about the underlined pathologies at the basis of sexual dysfunction.

Laboratory tests. A complete metabolic blood screening, as shown in table 3, is useful. Glycemia, total and HDL cholesterol, triglycerides, creatine, red cell count and urine analysis must be evaluated to discover some underlying systemic disease that can cause ED.

Table 3. Laboratory Test

Erectile Dysfunction	
I level	Glycoemia Total Cholesterol HDL-Cholesterol Triglycerides Red cell count Blood serum creatinine Urine analysis Hepatic function
II Level	Total Testosterone Luteinizing Hormone (LH) Follicle-Stimulating Hormone (FSH) Sex-Hormone Binding Globulin (SHBG) Prolactin Prostate Specified Antigen (PSA) Thyroid Stimulating Hormone

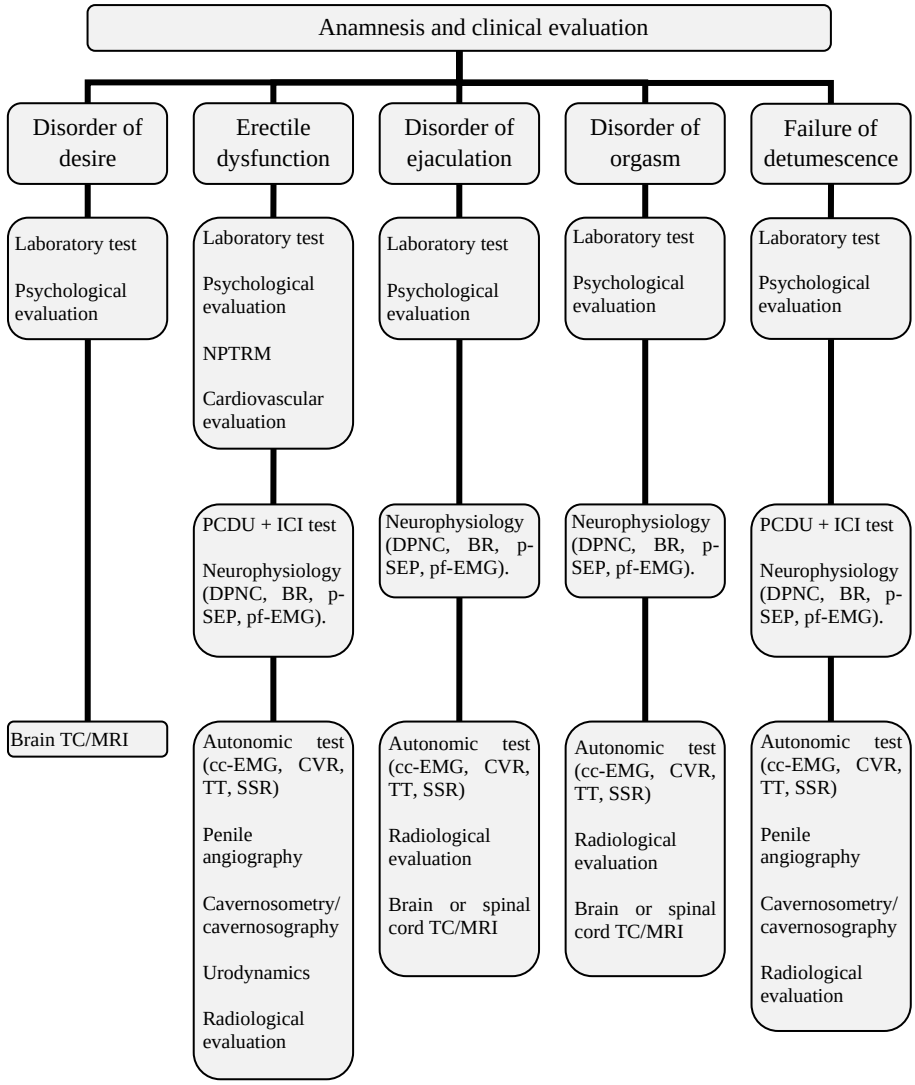


Figure 1. Clinical approach to neurological patients with sexual dysfunction.

Furthermore all patients must be evaluated for the presence of probable hypogonadism either primary (in the young) or secondary to other disease (in the elderly). The AUA recommends all patients with ED to be screened for all the sexual hormones involved in sexual function (i.e. testosterone, follicle stimulating hormone, LH and prolactin) and for albumin and sex hormone binding globulins, as they are the proteins binding the testosterone and could be useful to test the presence of free and bioavailable testosterone level [78]. According to EAU, a patient with ED could be assessed firstly only for the total amount of testosterone blood level (both free and bioavailable), then, if the testosterone level is low or borderline, the other sexual hormones and the binding proteins should be evaluated [79].

Prolactin screening is specifically recommended in hypogonadotropic hypogonadism and in hypoactive sexual desire.

All the subjects aged over 50 years have to be screened for the prostate specific antigen to detect the presence of an underlying prostate cancer or hyperplasia.

Thyroid Hormones determination completes the diagnostic blood examination when there is a clinical suspicion of a thyroid disease sometimes involved in sexual dysfunction.

Cardiovascular evaluation. The basic diagnostic approach is helpful to better assess the cardiovascular risk of patients suffering from ED. We have previously mentioned the relationship among ED and cardiovascular diseases (i.e. myocardial infarct, etc.) mainly due to the exposure to the same risk factors afflicting both the coronary arteries and the vessels providing blood supply to the penis. In the patients affected by a transient cerebrovascular disease without any evidence of cardiovascular symptoms, the presence of ED should be useful to deepen the cardiologic evaluation. This is helpful to better assess other cardiovascular risk factors and improve treatment options [26,43,80]. So, both *Electrocardiogram* and *Echocardiography* are useful for the evaluation of cardiovascular risk, especially for the possible use of phosphodiesterase inhibitors.

Nocturnal Penile Tumescence REM sleep Monitoring (NPTRM). It is well known that some erectile episodes are present during REM sleep. The neural mechanism of this sleep related erection (SRE) remains largely unknown. The involvement of several structures of the brainstem, acting directly on the spinal center of the erection, or on the hypothalamic (preoptic area), and other diencephalic structures was hypothesized . The screening of SRE through NPTRM is widespread used to differentiate the psychogenic ED from the organic one.

SRE consistency, reproducibility and their involuntary nature makes NPTRM a valuable technique for objectively assessing erectile capacity. Normal SRE suggests that the spinal cord, peripheral nerve, erectile tissue and immediate vascular supply at the end of the organ level are intact. By contrast, absence of SRE strongly suggests abnormal erectile pathophysiology.

The methodology of NPTRM is based on the recording of erection during sleep, monitoring circumference changes. To this purpose a strain gauge placed at both penile base and coronal sulcus is used. During recording, the patient has to be awakened at the time of maximal circumference increase in order to quantify rigidity using a buckling force device. This device is pressed against the tip of the penis and, applying an axial force, the pressure in grams force is recorded when the penis first begins to bend or buckle. At the same time patient and technician will be questioned on the erection percent of fullness. A scoring system made by Ware and Hirshkowitz [85] could help to define the SRE cycle, the criteria for maximum and partial erection, schema for tabulating fluctuations and pulsations, and procedures for incorporating measures of rigidity.

Thus NPTRM is useful to diagnose the psychogenic origin of ED. Unfortunately there are many difficulties in the right monitoring process. First of all, there is a disagreement about which normal values should be used for patients of different ages. NPTRM must be carried out in a sleep laboratory but at an expensive price due to the hospitalization of the patients. For this reason, laboratory testing is the favorite method for scientific investigation because it offers experimental control and it is studied with the investigation of the sleep stage, thus avoiding the possibility of false-positive or false-negative mainly due to home-made techniques (such as stamp bands that may break).

Consequently to the high cost of polysomnographic monitoring, a wide variety of alternative techniques has emerged and more sophisticated SRE home-monitoring, recording only the penile circumference, has evolved. Only one of these new system tests also circumferential compressibility to estimate rigidity, i.e. Rigiscan the most used device so far. Nevertheless, these devices do not assess sleep state; therefore, they are susceptible of false positive results (about 10-20% of monitoring) due to the finding of reduced SREs secondary to a disturbed REM sleep rather than to organic ED. In addition they rely on the patient's ability to properly place and use the device. To reduce or avoid these false positive results, it is recommended to make a monitoring in 3 different nights. This is mainly important to avoid the so-called "first night effect" (due to the novelty of the recording situation and the anxiety associated with it). In addition, three night recordings can help to improve the patient's ability in placing the device. Moreover, it can lead to a better evaluation of the SRE because of the large intraindividual difference in the increasing of the penile length during nocturnal erection [86]. Thereby, non-polysomnographic NPTRM are considered generally reliable for supporting true negative SRE tests.

NPTRM is a helpful evaluation for the diagnosis of psychogenic ED: although it does not provide certainty, a better result/deepening could be achieved with other techniques. For that reason, NOPTRM laboratory is more useful especially for scientific research [87]. A proposed guideline for clinical utilization of formal (polysomnographic) SRE evaluation is listed in Schmidt and Schmidt's review [88].

Penile Color Duplex Ultrasound (PCDU). When NPTRM is inconclusive a duplex ultrasound should be requested to investigate abnormalities or disease of penile vessels leading to ED and strengthening the suspicion of a psychogenic etiology of ED.

A basal PCDU can show arterial or venous abnormalities of the penis. First of all, it could highlight the presence of any arteriosclerotic plaque upon the surface of arteries supplying the penis and can give some information about the generalized vascular risk for atherosclerosis disease, especially in men without other risk factors. But a basal PCDU per se is not exhaustive for the identification of the whole typical vascular abnormalities in patients with ED, giving only information about the morphology of penile arteries but not about its haemodynamics. Thus a pharmacological test using the intracavernous injection (ICI) is mandatory. The ICI test is performed with the administration of a standard dose of a vasodilatator alprostadil (PGE1) directly inside the corpora cavernosa. The standard dose of PGE1 is 10 mg in middle-aged or elderly subject; in younger patients or in the presence of peripheral neuropathies the dosage could be decreased 2-5 mg in order to avoid priapism.

A dynamic PCDU, with ICI test, studies the hemodynamic changes occurring during pharmacological erection. A standard recording is performed at the peno-scrotal junction along an arterial segment corresponding to a Doppler angle of 55-65 degree to obtain comparable data at 5-10-15-20 minutes after ICI test. Attention must be polarized on three parameters: peak systolic velocity (PSV), end diastolic velocity (EDV) and resistive index (RI). When induced erection exceeds 3-h duration, it is recommended a pharmacological reverse with a 1-2 mg ethylephrine solution at 1:10 dilution direct into the corpora cavernosa, in order to prevent surgical detumescence.

Table 4. Colordoppler Ultrasound

Normal Values	ˇ maximum systolic velocity between 25-30 cm/sec ˇ end diastolic velocity < 5 cm/sec
Arteriogenic insufficiency	ˇ maximum systolic velocity < 25-30 cm/sec
Veno-occlusive dysfunction	ˇ maximum systolic velocity > 30 cm/sec ˇ end diastolic velocity > 5 cm/sec

In the presence of an ED due to vascular abnormalities (*see Table 4*), it is possible to find:

- PSV < 30 cm/sec
- EDV > 5 cm/sec
- RI < 0.8

PSV is important in the cases of arterial damage, recently modified with an age-adjusted value that permits to recognize an arteriogenic pathogenesis of ED and to detect peripheral vascular alteration in an ED population at a very early stage [26].

EDV could show a venous leakage, often characterized by a high false positive ratio for the presence of an EDV alteration in more than 50% of patients with normal erection. Moreover, anxiety-induced ED due to the procedures itself may influence EDV, so it may be helpful the repetition of PCDU using a Trimix solution (papaverine 0 mg + phentolamine 2 mg + alprostadil 20 mcg).

RI gives some information about smooth muscle cell relaxation and cavernous compliance such as priapism also useful to distinguish the high-flow from low-flow form. Furthermore, if associated with EDV, it could show a veno-occlusive mechanism in the genesis of ED perhaps at a superior level due to a minor influence of the probe-vessels angle than EDV alone [89].

Nevertheless, PCDU results should be cautiously interpreted before more invasive diagnostic testing. There is no need to continue the vascular investigation when PCDU is normal. However, a pathological value of PCDU parameters should lead to further investigation such as an arteriography and cavernosometry only for those patients who are considered potential candidates for vascular reconstructive surgery.

Whenever PCDU is not applicable or when there is contraindication or inefficiency of orally active drugs, the ICI test should be evaluated by clinical observation and palpation. It consists in five different degrees of response range from 0 (no sign of tumescence) to 4 (full penile rigidity with duration beyond 60 min). The test is positive whenever a grade from 0 to 2 occurs, although a positive test may be due to excessive sympathetic tone determined by high level of anxiety [43].

Neurophysiological testing. In patients affected by neurological disease and suffering of ED and/or ejaculatory disorders, a diagnosis of involvement of neural and muscular structures related to sexual function may be strengthened, refined and documented by neurophysiological testing. As previously explained, penile erection is elicited by central and peripheral structures and mediated by somatic and autonomic pathways. The ideal

neurophysiological assessment will objectively and qualitatively evaluate the functional status of all parts of this neurological network. In the last decades, several different methods have been developed, classified according to the neuroanatomical subsystem whose function they test. Therefore, it is possible to distinguish motor, sensory and autonomic tests.

Although the demonstration of nerve and/or muscle pathology by neurophysiological tests may confirm the diagnosis of nervous system involvement in the genesis of ED, these tests cannot themselves define ED as neurogenic because their abnormality per se has proven to be elusive. Nevertheless some tests, such as Dorsal Penile Nerve Conduction, Bulbocavernosus Reflex and pudendal Somatosensitive Evoked Potential (SEP), are classified as promising tools in evaluating patients with suspected neurogenic ED. Instead, tests measuring autonomic innervations and smooth muscle function would be of value in diagnosis, but their validity is at present not fully evaluated [80].

A basal standardized neurophysiological evaluation of all patients with ED includes the aforementioned tests exploring the somatic pathways.

The Dorsal Penile Nerve Conduction gives information about the speed of sensitive nerves conduction. It is an orthodromic sensitive nerve conduction performed by distending the penis and applying two electrodes to the extremities: the stimulating electrode is placed upon the glans, the detecting electrode at the basis of the penis with an interelectrode distance from 5.5 to 11.5 cm. A conduction defect, revealed by this test, can cause difficulty in maintaining erection during coitus.

The Bulbocavernosus Reflex assesses the latency of the sacral arc reflex. It is the neurophysiological correlate of the elicited bulbocavernosus reflex during the neurological examination, often requested when the response to physical stimuli is not clear. It is performed in men by stimulation of the dorsal penile nerve and detecting the response in the pelvic floor muscle through the aid of concentric single fiber needle Electromyography (EMG). Studies on its latency variability can be used to characterize the complexity of its central integration especially in suspected lesion of the sacral nerve, cauda equine or sacral spinal cord.

The pudendal-SEP evaluates the speed of conduction to cortex of stimuli applied at peripheral level with a percutaneous bipolar electrode placed on the penile shaft. The evoked potential is afterwards registered on the skull at the centrum with an average latency of 37 ms that is also length-dependent. Pudendal-SEP could give information whether the site of the lesion is peripheral or central. A rough discrimination among central and peripheral origin can be made by comparing pudendal-SEP and Tibial-SEP.

The normative values of Dorsal Penile Nerve Conduction, Bulbocavernosus Reflex and pudendal-SEP are shown in Table 5.

A whole neurophysiological assessment of patients suffering of ED with these three tests could be helpful to determine the site involved in the dysfunction (i.e. nerve, spinal cord, brainstem, etc.). But since these tests are insufficiently standardized and repeatable, only a few studies have been conducted on a large number of people. Moreover adequate training of the staff is rare in this field, and the tests are expensive and complicated. Thus, such neurological diagnostic tools have to be used only in specialized research institutes and in selected cases.

Further neurological specific investigation could show the involvement of the autonomic and motor system controlling the erection. These tests do not seem to be so helpful in the

diagnosis of ED so far, and to give only partial and unspecific information. As a matter of fact, they are often used as third level investigation and only in research protocols.

Pelvic Floor muscle EMG may be used to demonstrate activation patterns of striated muscles involved in the sexual response. EMG is the main diagnostic tool used to evaluate the motor component of the sexual response, since it differentiates normal from denervated and/or reinnervated muscle. It can be considered the method of choice to diagnose lower motor neuron involvement in the lower sacral segments, such as in cauda equine or lumbo-sacral injury. Unfortunately, this test is more sensitive to demyelination rather than axonal lesions which predominates in clinical practice.

Table 5. Penile neurophysiology

Normal Values	Velocity (m/sec)	Latency (msec)	Amplitude (μV)
Dorsal Penile Nerve	36.2 ± 3.2	2.34 ± 0.35	2.29 ± 1.08
Bulbocavernosus Reflex	—	35 ± 2 msec; range 28-42 *(Siroky et al)* 31 msec: average; range 24-40 *(Dick et al.)*	—
Pudendal SEP*	—	P1 onset: 35.2 ±3.0 P1 peak: 39.8 ± 1.9 N1 peak: 52.6 ± 2.6	—
Tibialis SEP (referred to scalp)	—	P1 peak: 38.5 ± 2.8 N1 peak: 48.1 ± 4.1 P2 peak: 61.2 ± 6.5 N2 peak: 79.7 ± 9.4	P1: 1.1 ± 0.3 N1: 1.4 ± 0.5 P2: 1.8 ± 0.4 N2: 21 ± 0.6

* Always in comparison with Tibialis SEP.

P1 = first positive peak; P2 = second positive peak; N1 = first negative peak; N2 = second negative peak.

The autonomic tests are less reliable than somatic ones, due to their indirect measurement with many confounding factors (such as medication, caffeine, temperatures, etc) and to the absence of valid and reproducible characteristics. Commonly the following four different tests are used to explore neurovegetative pathways.

Corpus Cavernosum EMG (cc-EMG) is the most direct method to examine vasomotor integrity. It could be assessed by applying superficial needle in the corpora cavernosa. The use of Gal-surface electrodes at both sides of the corpora or a non-insulated needle is also possible, but the registration can be confused with other electrophysiological activities such as skin response. The record is performed in the flaccid state, during erection and then detumescence. So, cc-EMG is counted as a valuable tool in assessing the contribution of autonomic neuropathy and trabecular muscle degeneration to erectile dysfunction linked to a sympathetic impairment.

Sympathetic Skin Response (SSR) explores the sudomotor sympathetic unmyelinated C-fibers innervating the sweat glands of the whole body. Potentials are measured with surface electrodes placed upon skin areas with different sweat glands densities. Its interpretation is

under debate also due to the influence of many confounding factors and its poor specificity for the genital area. Because SSR does not evaluate parasympathetic or motor sympathetic fibers that mediate most clinical symptoms of neuropathy, absence of SSR does not necessarily correlate with complaints of autonomic neuropathy.

Thermal Threshold Testing (TTT) gives information on afferent small fibers and, thereby, indirectly on autonomic nerve fibers. The test is performed with use of a Peltier-element applied to skin which leads temperature stimuli. There are three different methods to achieve TTT, each one regularly used in clinical practice: two forced choice method, method of limit, staircase method. All parts of the body could be tested for TTT, thereby revealing information on length-dependent small fiber autonomic neuropathy.

Cardiovascular Reflex Tests (CVR) assess variation in heart rate and blood pressure In response to various stimuli such as forced breathing, standing up or tilting, Valsalva's maneuver, sustained isometric handgrip, mental arithmetic task and cold pressure. Sex and age dependency of reference values are still in debate. CVR explores the parasympathetic function through the variation on the heart rate, while blood pressure variations reflect sympathetic function.

For physiological reason cc-EMG is the favorite diagnostic tool for examining the whole vegetative system involved in erection. Other kinds of examinations are indicated to refine and confirm diagnosis of neuropathy with altered neurovegetative function. So, in the cases of length-dependent neuropathy SSR and TTT are applicable, instead in the case of length independent neuropathy CVR is generally accepted [90].

Penile Angiography, Cavernosometry and Cavernosography. These three diagnostic tools are considered as third level investigations to better evaluate arterial and venous pathologies. They are used only when PCDU exam is inconclusive to refine the diagnosis of a vascular and especially in young subjects that are candidate for surgical repair.

The Penile Angiography is performed when an arterial obstruction is suspected to better define the anatomic pattern of arterial occlusive disease, so to allow the planning of an appropriate vascular surgical approach. In the past, before the advent of PCDU, arteriography of the penile arteries was considered the gold standard for assessing the pathogenesis of a vascular ED. To date, angiography is advised only in two conditions: to map the arteries in the lower limbs prior to a revascularization procedure and to confirm a diagnosis of high-flow priapism. This method provides precise anatomical data but does not permit the assessment of functional changes consequent to the erection. For that, it is more helpful to perform the Cavernous Artery Occlusion Pressure during the cavernosometry time, by measuring the occlusion pressure of cavernous artery. With a Doppler ultrasound probe placed at the basis of the penis, it is possible to detect the value of pressure which could reestablish the cavernous artery pulsating flow after the injection of a saline solution directly inside the corpora cavernosa. A difference over 36 mmHg between brachial and cavernous systolic occlusion pressure is considered as abnormal cavernous artery hemodynamic function.

Cavernosometry and Cavernosography are instead useful for the assessment of the venous dysfunction in patients with ED. Cavernosometry evaluates the presence of a low resistance to a venous outflow due to anatomic (such as large and ectopic veins exiting the cavernous corpora) or functional abnormalities (such as limited capacitor function of the corpora). In particular, venous outflow resistance is assessed by determining the intracavernous smooth muscle relaxation through the ICI test. The state of complete cavernous pressure is characterized by a linear relationship between infusion rate and

intracavernous pressure after ICI at 30, 60, 90, 120 and 150 mmHg. The most used parameters to measure venous resistance are maintenance flow (MV), pressure loss (PL) and the pressure volume response (PVR). All of these three indexes have some technical bias: PL and PVR depend not only on the tissue properties of the corpora cavernosa but also on cavernous arterial pressure; MF is age depending and the relationship among age and MF properties is not well studied so far. Detailed discussion on these parameters and their implication is beyond the scope of this book and can be found elsewhere.

Cavernosography, instead, can detect the exact anatomic site of the leakage through the infusion of a nonallergic contrast medium of low osmolality. The anatomic site of draining veins is then realtime visualized fluoroscopically with an anteroposterior and right and left oblique projection. In the cases of a veno-occlusive dysfunction, during the erection the veins are visualized draining directly from the corpora in the glans, corpus spongiosum, the deep dorsal, cavernous and crural veins. More than one part could be involved in the same patient with the deep dorsal and cavernous veins as the most common combination [43,89].

Ancillary Test. This term is here used to group all those tests that are not necessary for the diagnosis of a sexual dysfunction but helpful to refine or confirm it.

The ancillary tests include the whole radiological evaluation of the organs acting on the sexual function. The anatomical evaluation of the urogenital apparatus through ultrasounds should be performed to better assess and manage the possible presence of a specific disease. The confirmation of the diagnosis should be made with a further CT scan or MRI of the pelvis and genitalia.

For a complete urological evaluation, patients suffering with sexual dysfunction secondary to a disease of the lower urinary tract should perform an Urodynamics evaluation to explore the urinary flow rate, the bladder capacity and the size of the residual volume, the bladder pressure, and the presence or flow assessment under fluoroscopic imaging. All these diagnostic tools are helpful in the diagnosis of the diseases involved in the aforementioned LUTS (i.e. prostate and bladder cancer). The urodynamic evaluation is often followed by further specific and more invasive urological evaluation as intravenous urography and nuclear medicine diagnostic tests (such as static and dynamic isotope renography). Those techniques are most important in the elderly for their more frequent association among LUTS and sexual dysfunction [78,91].

Lastly, a CT and MRI examination of the brain and/or spinal cord could be helpful to determine the exact diagnosis of the disease presented with sexual problems. So, it is possible to show the presence of a demyelinated area in the cases of Multiple Sclerosis, or the presence of the lesion in the brain or spinal cord in the cases of trauma, stroke, etc.

Conclusion

Sexuality is an aspect of an individual’s life which is growing more and more important. Great attention on sexual function is paid worldwide by young, adult, and even elderly men. Thus all medical doctors should be informed about sexual disorders and discuss them with their patients.

Sexual function could be altered in many medical conditions. The most common sexual dysfunctions in neurological diseases are ED and ejaculation problems, due to a direct injury of the nervous centre and/or of the peripheral nerve.

Evaluation of sexual functions should be an integrative part of the neurological examination since the improvement of sexual life in patients with neurological disorders could improve their self-esteem and quality of life.

References

[1] Kandeel FR, Koussa VK, Swerdloff RS. Male sexual function and its disorders: physiology, pathophysiology, clinical investigation, and treatment. *Endocrine Reviews.* 2001;22:342-88

[2] Lue TF. Erectile dysfunction. *The New England Journal Medicine*. 2000;342:1802-13

[3] Wessells H, Lue TF, McAninch JW.Penile length in the flaccid and erect states: guidelines for penile augmentation. *The Journal of Urolology*. 1996;156:995-7.

[4] Burnett AL. Nitric oxide in the penis: physiology and pathology. *The Journal of Urolology*. 1997;157:320-4

[5] Lowenstein CJ, Dinerman JL, Snyder SH. Nitric oxide: a physiologic messenger. *Annals of Internal Medicine*. 1994;120:227-37.

[6] American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 4th ed: DSM-IV. Washington (DC), 1995.

[7] World Health Organization. International Classification of Diseases and related health problems: ICD-10. Geneva, 1992.

[8] National Institutes of Health. NIH Consensus Conference: Impotence. (NIH Consensus Statement 1992;10(4):1-31). *Journal of American Medical Association* 1993:83-90.

[9] Basson R, Schultz WW. Sexual sequelae of general medical disorders. *Lancet*. 2007;369:409-24.

[10] Benet AE, Melman A. The epidemiology of erectile dysfunction. *The Urologic Clinics of North America.* 1995 ; 22:699-709.

[11] Schiavi RC, Segraves RT. The biology of sexual function. *The Psychiatric Clinics of North America*. 1995 ;18:7-23.

[12] Salmimies P, Kockott G, Pirke KM, Vogt HJ, Schill WB. Effects of testosterone replacement on sexual behavior in hypogonadal men. *Archives of Sexual Behavior*. 1982;11:345-53

[13] Levine SB. The psychological evaluation and therapy of psychogenic impotence. In: Seagraves RT, Schoenberg HW (eds) Diagnosis and Treatment of Erectile Disturbances: A guide for Clinicians. Plenum Medical Book Co., New York, NY, pp 87-104.

[14] Hawton K. Sex Therapy: A Pratical Guide. Oxford University Press, New York, NY, pp 123-199.

[15] Koller WC, Vetere-Overfield B, Williamson A, Busenbark K, Nash J, Parrish D. Sexual dysfunction in Parkinson's disease. *Clinical Neuropharmacology*. 1990;13:461-3

[16] Powers JM, Schaumburg HH. A fatal cause of sexual inadequacy in men: adreno-leukodystrophy. *The Journal of Urology.* 1980;124:583-5

[17] Toone BK, Edeh J, Nanjee MN, Wheeler M. Hyposexuality and epilepsy: a community survey of hormonal and behavioural changes in male epileptics. *Psychological Medicine*. 1989;19:937-43.

[18] Walsh PC, Wilson JD. Impotence and infertility in men. In: Braumwald E, Isselbacher KJ, PetersdorfRS, Wilson JD, Martin JB, Fauci AS (eds) Harrison's Principals of Internal Medicine, ed 15. McGraw-Hill Book Co., New York, NY, pp 217-220.

[19] Harvey KV, Balon R. Clinical implications of antidepressant drug effects on sexual function. Ann Clin Psychiatry. 1995;7:189-201.

[20] Finger WW, Lund M, Slagle MA. Medications that may contribute to sexual disorders. A guide to assessment and treatment in family practice. *The Journal of Family Practice*. 1997;44:33-43.

[21] Impotence. NIH Consensus Conference Statement, 10:1, 1992.

[22] Basson R, Schultz WW. Sexual sequelae of general medical disorders. *Lancet*. 2007;369:409-24.

[23] Petrone L, Mannucci E, Corona G, Bartolini M, Forti G, Giommi R, Maggi M. Structured interview on erectile dysfunction (SIEDY): a new, multidimensional instrument for quantification of pathogenetic issues on erectile dysfunction. *International Journal of Impotence Research*. 2003;15:210-20.

[24] Thompson IM, Tangen CM, Goodman PJ, Probstfield JL, Moinpour CM, Coltman CA. Erectile dysfunction and subsequent cardiovascular disease. *JAMA: the Journal of American Medical Association*. 2005 21;294:2996-3002.

[25] Bhasin S, Cunningham GR, Hayes FJ, Matsumoto AM, Snyder PJ, Swerdloff RS, Montori VM. Testosterone therapy in adult men with androgen deficiency syndromes: an endocrine society clinical practice guideline. *The Journal of Clinical Endocrinology and Metabolism*. 2006 ;91:1995-2010.

[26] Foresta C, Caretta N, Corona G, Fabbri A, Francavilla S, Jannini E, Maggi M, Bettocchi C, Lenzi A. Clinical and metabolic evaluation of subjects with erectile dysfunction: a review with a proposal flowchart. *International Journal of Andrology*. 2009 ;32:198-211.

[27] Vlachopoulos C, Rokkas K, Ioakeimidis N, Stefanadis C. Inflammation, metabolic syndrome, erectile dysfunction, and coronary artery disease: common links. *European Urolology*. 2007 ;52:1590-600.

[28] Watts GF, Chew KK, Stuckey BG. The erectile-endothelial dysfunction nexus: new opportunities for cardiovascular risk prevention. *Nature Clinical Practice. Cardiovascular medicine*. 2007;4:263-73.

[29] Corona G, Mannucci E, Petrone L, Balercia G, Paggi F, Fisher AD, Lotti F, Chiarini V, Fedele D, Forti G, Maggi M. NCEP-ATPIII-defined metabolic syndrome, type 2 diabetes mellitus, and prevalence of hypogonadism in male patients with sexual dysfunction. *The Journal of Sexual Medicine*. 2007;4:1038-45.

[30] Nicolosi A, Laumann EO, Glasser DB, Moreira ED Jr, Paik A, Gingell C; Global Study of Sexual Attitudes and Behaviors Investigators' Group. Sexual behavior and sexual dysfunctions after age 40: the global study of sexual attitudes and behaviors. *Urology*. 2004;64:991-7.

[31] Lindau ST, Schumm LP, Laumann EO, Levinson W, O'Muircheartaigh CA, Waite LJ. A study of sexuality and health among older adults in the United States. *The New England Journal Medicine*. 2007 ;357:762-74.

[32] Nicolosi A, Glasser DB, Moreira ED, Villa M; Erectile Dysfunction Epidemiology Cross National Study Group. Prevalence of erectile dysfunction and associated factors among men without concomitant diseases: a population study. *International Journal of Impotence Research*. 2003;15:253-7.

[33] Schiavi RC, Rehman J. Sexuality and aging. Urol Clin North Am. 1995 ;22:711-26.

[34] Isidori AM, Giannetta E, Gianfrilli D, Greco EA, Bonifacio V, Aversa A, Isidori A, Fabbri A, Lenzi A. Effects of testosterone on sexual function in men: results of a meta-analysis. Clin Endocrinol. 2005;63:381-94.

[35] Gray PB, Singh AB, Woodhouse LJ, Storer TW, Casaburi R, Dzekov J, Dzekov C, Sinha-Hikim I, Bhasin S. Dose-dependent effects of testosterone on sexual function, mood, and visuospatial cognition in older men. *The Journal of Clinical Endocrinology and Metabolism*. 2005;90:3838-46.

[36] Morelli A, Filippi S, Mancina R, Luconi M, Vignozzi L, Marini M, Orlando C, Vannelli GB, Aversa A, Natali A, Forti G, Giorgi M, Jannini EA, Ledda F, Maggi M. Androgens regulate phosphodiesterase type 5 expression and functional activity in corpora cavernosa. *Endocrinology*. 2004;145:2253-63.

[37] Vignozzi L, Corona G, Petrone L, Filippi S, Morelli AM, Forti G, Maggi M. Testosterone and sexual activity. *Journal of Endocrinological Investigation*. 2005;28(3 Suppl):39-44.

[38] Morelli A, Corona G, Filippi S, Ambrosini S, Forti G, Vignozzi L, Maggi M. Which patients with sexual dysfunction are suitable for testosterone replacement therapy? *Journal of Endocrinological Investigation.* 2007; 30:880-8.

[39] Esposito K, Giugliano F, Martedì E, Feola G, Marfella R, D'Armiento M, Giugliano D. High proportions of erectile dysfunction in men with the metabolic syndrome. *Diabetes Care*. 2005;28:1201-3

[40] Kapoor D, Malkin CJ, Channer KS, Jones TH. Androgens, insulin resistance and vascular disease in men. *Clinical Endocrinology*. 2005;63:239-50.

[41] Corona G, Mannucci E, Petrone L, Schulman C, Balercia G, Fisher AD, Chiarini V, Forti G, Maggi M. A comparison of NCEP-ATPIII and IDF metabolic syndrome definitions with relation to metabolic syndrome-associated sexual dysfunction. *The Journal of Sexual Medicine*. 2007;4:789-96

[42] Gazzaruso C, Giordanetti S, De Amici E, Bertone G, Falcone C, Geroldi D, Fratino P, Solerte SB, Garzaniti A. Relationship between erectile dysfunction and silent myocardial ischemia in apparently uncomplicated type 2 diabetic patients. *Circulation*. 2004 ;110:22-6.

[43] Foresta C, Caretta N, Aversa A, Bettocchi C, Corona G, Mariani S, Rossato M. Erectile dysfunction: symptom or disease? *Journal of Endocrinological Investigation*. 2004;27:80-95.

[44] Kaiser DR, Billups K, Mason C, Wetterling R, Lundberg JL, Bank AJ. Impaired brachial artery endothelium-dependent and -independent vasodilation in men with erectile dysfunction and no other clinical cardiovascular disease. *The Journal of the American College of Cardiology*. 2004;4:179-84.

[45] Seidell JC, Björntorp P, Sjöström L, Kvist H, Sannerstedt R. Visceral fat accumulation in men is positively associated with insulin, glucose, and C-peptide levels, but negatively with testosterone levels. *Metabolism*. 1990; 39:897-901

[46] Isidori AM, Caprio M, Strollo F, Moretti C, Frajese G, Isidori A, Fabbri A. Leptin and androgens in male obesity: evidence for leptin contribution to reduced androgen levels. *The Journal of Clinical Endocrinology and Metabolism*. 1999;84:3673-80

[47] Kalyani RR, Dobs AS. Androgen deficiency, diabetes, and the metabolic syndrome in men. *Current Opinion in Endocrinology, Diabetes, and Obesity*. 2007;14:226-34.

[48] Rosen R, Altwein J, Boyle P, Kirby RS, Lukacs B, Meuleman E, O'Leary MP, Puppo P, Robertson C, Giuliano F. Lower urinary tract symptoms and male sexual dysfunction: the multinational survey of the aging male (MSAM-7). *European Urolology*. 2003;44:637-49

[49] McVary KT. Erectile dysfunction and lower urinary tract symptoms secondary to BPH. *European Urolology*. 2005;47:838-45.

[50] McConnell JD, Roehrborn CG, Bautista OM, Andriole GL Jr, Dixon CM, Kusek JW, Lepor H, McVary KT, Nyberg LM Jr, Clarke HS, Crawford ED, Diokno A, Foley JP, Foster HE, Jacobs SC, Kaplan SA, Kreder KJ, Lieber MM, Lucia MS, Miller GJ, Menon M, Milam DF, Ramsdell JW, Schenkman NS, Slawin KM, Smith JA; Medical Therapy of Prostatic Symptoms (MTOPS) Research Group. The long-term effect of doxazosin, finasteride, and combination therapy on the clinical progression of benign prostatic hyperplasia. *The New England Journal Medicine*. 2003;349:2387-98.

[51] Sachs BD. The false organic-psychogenic distinction and related problems in the classification of erectile dysfunction. *International Journal of Impotence Research*. 2003;15:72-8.

[52] Sáenz de Tejada I, Angulo J, Cellek S, González-Cadavid N, Heaton J, Pickard R, Simonsen U. Pathophysiology of erectile dysfunction. *The Journal of Sexual Medicine*. 2005;2:26-39

[53] Bors E, Comarr AE. Neurological urology: physiology of micturition, its neurological disorders and sequelae. Baltimore: Univeristiy Park Press; 1971.

[54] Siegel T, Moul JW, Spevak M, Alvord WG, Costabile RA. The development of erectile dysfunction in men treated for prostate cancer. *The Journal of Urolology*.2001;16:430-5

[55] Fazio L, Brock G. Erectile dysfunction: management update. *CMAJ : Canadian Medical Association journal*. 2004;170:1429-37.

[56] Richardson JD. Male sexual dysfunction. Ejaculatory problems. *Australian Family Physician*. 1993;22:1367-70, 1372.

[57] Metz ME, Pryor JL. Premature ejaculation: a psychophysiological approach for assessment and management. *Journal of Sex and Marital Therapy*. 2000;26:293-320.

[58] Bettocchi C, Verze P, Palumbo F, Arcaniolo D, Mirone V. Ejaculatory disorders: pathophysiology and management. *Nature Clinical Practice Urology*. 2008 ;5:93-103.

[59] Ohl DA, Quallich SA, Sønksen J, Brackett NL, Lynne CM. Anejaculation and retrograde ejaculation. *Urologic Clinics of North America*. 2008;35:211-20, viii.

[60] Kaplan HS. Post-ejaculatory pain syndrome. *Journal of Sex and Marital Therapy*. 1993 Summer;19(2):91-103.

[61] Aizenberg D, Zemishlany Z, Hermesh H, Karp L, Weizman A. Painful ejaculation associated with antidepressants in four patients. *The Journal of Clinical Psychiatry*. 1991;52:461-3

[62] Barnas J, Parker M, Guhring P, Mulhall JP. The utility of tamsulosin in the management of orgasm-associated pain: a pilot analysis. *European Urolology*. 2005;47:361-5.

[63] Barnas JL, Pierpaoli S, Ladd P, Valenzuela R, Aviv N, Parker M, Waters WB, Flanigan RC, Mulhall JP. The prevalence and nature of orgasmic dysfunction after radical prostatectomy. *BJU International*. 2004; 94:603-5.

[64] Robert R, Prat-Pradal D, Labat JJ, Bensignor M, Raoul S, Rebai R, Leborgne J. Anatomic basis of chronic perineal pain: role of the pudendal nerve. *Surgical and Radiologic Anatomy*. 1998;20:93-8

[65] Myers RP. An anatomic approach to the pelvis in the male. In Crawford ED, Das S eds, Current Genitourinary Cancer Surgery, 2nd edn. Baltimore: Williams and Wilkins, 1997: 55-69.

[66] Shafik A. Re: Neurourological insights into the etiology of genitourinary pain in men. *The Journal of Urolology*. 1999;162:2106-7.

[67] Hetrick DC, Ciol MA, Rothman I, Turner JA, Frest M, Berger RE. Musculoskeletal dysfunction in men with chronic pelvic pain syndrome type III: a case-control study. *The Journal of Urolology*. 2003;170:828-31

[68] Ferguson JM. The effects of antidepressants on sexual functioning in depressed patients: a review. *The Journal of Clinical Psychiatry*. 2001;62 Suppl 3:22-34.

[69] Segraves RT. Effects of psychotropic drugs on human erection and ejaculation. *Archives of General Psychiatry*. 1989;46:275-84.

[70] Ilie CP, Mischianu DL, Pemberton RJ. Painful ejaculation. *BJU International*. 2007 Jun;99(6):1335-9.

[71] Beutel ME, Weidner W, Brähler E. Epidemiology of sexual dysfunction in the male population. *Andrologia*. 2006;38:115-21.

[72] Levine JF, Saenz de Tejada I, Payton TR, Goldstein I. Recurrent prolonged erections and priapism as a sequela of priapism: pathophysiology and management. *The Journal of Urolology*. 1991;145:764-7

[73] Lue TF, Hellstrom WJ, McAninch JW, Tanagho EA. Priapism: a refined approach to diagnosis and treatment. *The Journal of Urolology*. 1986;136:104-8.

[74] Erection and priapism: a new physiopathological concept. Hauri D, Spycher M, Brühlmann W. *Urologia Internationalis*. 1983;38:138-45

[75] Burt FB, Schirmer HK, Scott WW. A new concept in the management of priapism. *The Journal of Urolology*. 1960;83:60-1.

[76] Nelson JH 3rd, Winter CC. Priapism: evolution of management in 48 patients in a 22-year series. *The Journal of Urolology*. 1977;117:455-8

[77] Burnett AL. Priapism pathophysiology: clues to prevention. *International Journal of Impotence Research*. 2003;15 Suppl 5:S80-5.

[78] Montague DK, Jarow JP, Broderick GA, Dmochowski RR, Heaton JPW, Lue TF, Milbank AJ, Nehra A, Sharlip ID; Members of the erectile dysfunction guideline update panel. Chapter 1: The Management Of Erectile ysfunction: An AUA Update. *The Journal of Urolology*. 2005; 174:230-39

[79] Wespes E, Amar E, Hatzichristou D, Hatzimouratidis K, Montorsi F, Pryor J, Vardi Y; EAU members. EAU Guidelines on erectile dysfunction: an update. *European Urolology*. 2006;49:806-15.

[80] Lundberg PO, Ertekin C, Ghezzi A, Swash M, Vodusek D. Neurosexology. Guidelines for Neurologists. European Federation of Neurological Societies Task Force on Neurosexology. *European Journal of Neurology* 2001, 8 (suppl 3):2-24.

[81] O'Leary MP, Fowler FJ, Lenderking WR, Barber B, Sagnier PP, Guess HA, Barry MJ. A brief male sexual function inventory for urology. *Urology*. 1995;46:697-706

[82] Rosen RC, Riley A, Wagner G, Osterloh IH, Kirkpatrick J, Mishra A. The international index of erectile function (IIEF): a multidimensional scale for assessment of erectile dysfunction. *Urology*. 1997 Jun;49(6):822-30.

[83] Lue TF. Editorial Comment. *The Journal of Urolology*. 1996; 156:552

[84] Steers WD. Neural pathways and central sites involved in penile erection: neuroanatomy and clinical implications. *Neuroscience and Biobehavioral Reviews*. 2000;24:507-16.

[85] Ware JC, Hirshkowitz M. *Monitoring penile erection during sleep.* In: Kryger MH, Roth T, Dement WC. *Principle and practice of sleep medicine.* Philadelphia: Saunders WB; 1994. p. 967-77

[86] Wasserman MD, Pollak CP, Spielman AJ, Weitzman ED. Theoretical and technical problems in the measurement of nocturnal penile tumescence for the differential diagnosis of impotence. *Psychosomatic Medicine*. 1980;42:575-85

[87] Hirshkowitz M, Schmidt MH.Sleep-related erections: clinical perspectives and neural mechanisms. *Sleep Medicine Reviews.* 2005;9:311-29.

[88] Schmidt MH, Schmidt HS. Sleep-related erections: neural mechanisms and clinical significance. *Current Neurology and Neuroscience Reports*. 2004;4:170-8.

[89] Meuleman EJ, Diemont WL. Investigation of erectile dysfunction. Diagnostic testing for vascular factors in erectile dysfunction. *Urologic Clinics of North America*. 1995;22:803-19.

[90] Diemont WL, Meuleman EJ. Neurological testing in erectile dysfunction. *Journal of Andrology*. 1997;18:345-50.

[91] Whitfield HN. ABC of urology: Urological evaluation. *British Medical Journal*. 2006 ;333:432-5.

In: Male Sexual Dysfunctions in Neurological Diseases… ISBN 978-1-61761-855-0
Editor: Calabrò Rocco Salvatore

Chapter 4

Sexual Dysfunction and Epilepsy

Rocco Salvatore Calabrò and Adriana Magaudda

Abstract

The association between epilepsy and sexual disorders has long been known. However, the etiology remains uncertain, but it is likely to be multifactorial in origin involving neurological, endocrine, iatrogenic, psychiatric and psychosocial factors. Two kinds of sexual disorders associated with epilepsy can be distinguished: those which are directly related to seizures (ictal) and those unrelated in time to seizure occurrence (interictal). The most common sexual dysfunction is hyposexuality, even if hypersexuality and different paraphilias have been reported. Here prevalence, etiology, diagnosis and treatment of male sexual dysfunction in epilepsy are discussed in order to improve clinical management of the epileptic patient.

Introduction

Epilepsy (from the Ancient Greek επιληψία *epilēpsía*) is a common chronic neurological disorder characterized by recurrent unprovoked seizures. These seizures are transient signs and/or symptoms of abnormal, excessive or synchronous neuronal activity potentially involving all the brain areas.

In partial seizures the electrical disturbance is limited to a specific area of one cerebral hemisphere. These seizures are subdivided into simple partial ones (when consciousness is retained) and complex partial ones (when consciousness is impaired or lost). Generalized seizures affect both cerebral hemispheres from the beginning of the seizure. They produce loss of consciousness, either briefly or for a longer period of time, and are sub-categorized into several major types: generalized tonic clonic; myoclonic; absence; and atonic.

Classification of seizures and common seizures patterns are shown in table 1 and 2, respectively.

Table 1. International Classification of Epileptic Seizures

I. Generalized seizures (bilaterally symmetrical and without local onset)
- A. Tonic, clonic or tonic-clonic (grand mal)
- B. Absence:
  - With loss of consciousness only
  - Complex – with brief tonic, clonic or automatic movements
- C. Lennox-Gestaut Syndrome
- D. Juvenile myoclonic epilepsy
- E. Infantile spasms (West syndrome)
- F. Atonic (astatic, akinetic) seizures (sometimes with myoclonic jerks)

II. Partial, or focal, seizures (seizures beginning locally)
- A. Simple (without loss of consciousness or alteration in psychic function)
  - Motor – Frontal lobe origin (tonic, clonic, tonic-clonic; jacksonian; benign childhood epilepsy; epilepsia partialis continua)
  - Somatosensory or special sensory (visual, auditory, olfactory, gustatory or vertiginous)
- B. Autonomic
- C. Pure psychic
- D. Complex (with impaired consciousness)
- E. Beginning as simple partial seizures and progressing to impairment of consciousness
- F. With impairment of consciousness at onset

III. Specific epileptic syndromes
- A. Myoclonus and myoclonic seizures
- B. Reflex epilepsy
- C. Acquired aphasia with convulsive disorder
- D. Febrile and other seizures of infancy and childhood
- E. Hysterical seizures

About 50 million people worldwide have epilepsy, with almost 90% of these people being in developing countries. Epilepsy is more likely to occur in young children or people over the age of 65; however it can occur at any time. Epilepsy is usually controlled, but not cured, with specific medications (i.e. antiepileptic drugs), although surgery may be considered in difficult cases (about 30%). Not all epilepsy syndromes are lifelong since some forms are confined to particular stages of childhood. Epilepsy should not be understood as a single disorder, but rather as syndromic with vastly divergent symptoms, different EEG patterns, outcomes and response to treatment.

Over the past decade there has been increased interest in how epilepsy and its treatment affect the quality of life (QOL) of epilepsy patients. Epilepsy is unique among chronic neurologic diseases in its potential influence on QOL. Epilepsy often begins at young age and may hinder social and cognitive development. In addition, epilepsy is episodic, occurs unpredictably and typically involves loss of consciousness, leading to driving and employment restrictions and is associated with high rates of psychiatric comorbidity. Studies have indicated that compared with the general population, people with epilepsy have more psychological problems [1]. Common nonmedical problems include feelings of stigma, psychological distress, unemployment, lowered self-esteem, and interpersonal difficulties including social isolation and low social competence [2-3]. Among medical problems, psychiatric comorbidity, effect of antiepileptics, duration of disease and, above all, frequency of seizures, are considered the most relevant determinants of poor QOL scores [4-5].

Table 2. Common seizure patterns

Clinical Type	Localization
Somatic Motor	
– Jacksonian (focal motor)	Prerolandic gyrus
– Masticatory, salivation, speech arrest	Amygdaloid nuclei
– Simple contraversive	Frontal
– Head and eye turning associated with arm movement or athetoid-dystonic postures	Supplementary motor cortex
Somatic and special sensory (auras)	
Somatosensory	Controlateral postrolandic
– Unformed images, lights, patterns	Occipital
– Auditory	Heschl's gyri
– Vertiginous	Superior temporal
– Olfactory	Mesial temporal
– Gustatory	Insula
– Visceral: autonomic	Insular-orbital-frontal cortex
Complex partial seizures	
Formed hallucinations	Temporal neocortex or amygdaloid-hippocampal complex
Illusion	
– Dyscognitive experiences (dejà-vù, dreamy state, depersonalization)	
– Affective States (fear, depression or elation)	Temporal
– Automatism (ictal and postictal)	Temporal and frontal
Absence	Frontal cortex, amygdaloid-hippocampal complex, reticular-cortical system
Bilateral epileptic myoclonus	Reticulocortical, frontocentral

Sexual Dysfunction in Epileptic Male Patient

Sexual health is one of the most important aspects of QOL and it is often impaired in epileptic patients. Sexual disorders associated with epilepsy can be directly related to seizures (ictal), or unrelated in time to seizures occurrence (interictal).

Seizures may also be provoked by "normal" sexual activity.

Ictal Sexual Disorders

Genital and sexual manifestations are rare clinical phenomena during or after complex partial seizures and can be subdivided into sexual auras, sexual automatisms, genital auras and genital automatisms, where "sexual" refers to the symptoms/signs with erotic content while "genital" refers to symptoms/signs involving genitals but without erotic meaning [6].

Genital auras are sensations like numbness, tingling and pain in the genitals and indicate epileptic discharges in the postcentral gyrus, interemispheric fissure and perisylvian region [7].

Sexual auras are commonly experienced as pleasant erotic feelings or thoughts and sometimes can be accompanied by sexual arousal and orgasm; they can be associated with temporal lobe epilepsy (TLE) and they seem to occur predominantly in women [7].

Given that spontaneous sexual ictal thoughts and feelings are extremely common in men, ictal experiences may be unnoticed.

Genital automatisms consist of rubbing, scratching and fondling of the genitals, and occur mostly in patients with TLE, while Sexual automatisms, i.e. hypermotoric pelvic thrusting eventually combined with masturbation, are thought to be linked to epileptogenic activity within the frontal lobe [8].

Seizures induced by orgasm are very rare with right hemisphere and female dominance which suggests a different neural organization of psychosexual behavior between male and female brains [9].

Interictal Disorders

Epilepsy has been described in association with self-mutilation, transvestitism, sadomasochism, exhibitionism and fetishism and these sexual disorders may be resolved with the cessation of attacks through medical or surgical treatment [10]. Hypersexuality, i.e. excessive sexual activity which produces no lasting relief or satisfaction has been occasionally reported.

However the most common sexual dysfunction in epileptic patients is hyposexuality, defined as "a global reduction in sexual interest, awareness and activity".

Prevalence of Sexual Dysfunction

Gastaut [11] was the first author to underline the association between sexual dysfunction and epilepsy. In his uncontrolled study, he found a global hyposexuality in over two-thirds of patients with temporal lobe epilepsy (TLE). Since then many studies have been performed in epileptic men with regard to partial epilepsy (PE), showing rates of sexual dysfunction from 22% to 67%.

The dysfunction most often mentioned includes reduced potency, decreased desire and impaired sexual performance even if it has been suggested that epilepsy interferes specifically with physiological function while sexual desire remains unaffected [12].

Taylor [13] reported hyposexuality and erectile dysfunction (ED) in about 80 percent of his patients while Toone *et al* [14] found that 57% of men with epilepsy had experienced erectile failure compared with 18% of the control group. There has not been a consensus regarding the prevalence of ED which varies within particular epileptic patients with a

frequency as low as 3% in outpatients to as high as 58% in patients evaluated for epilepsy surgery [15]. Moreover, epileptic men have been found to have an increased risk of ED of up to 57% compared to 3-9% in the general population [16].

A recent study by Nikoobakht *et al* has shown an ED prevalence of 42% in a sample of epileptic outpatients. Authors' findings were also indicative of frequent impairment of orgasmic phase and sexual desire especially in patients with partial seizures [17].

Other workers have not found this degree of dysfunction. Indeed, Jensen et al reported that only 8% of men with epilepsy had sexual disorders compared with 13% of controls. Patients experienced sexual desire 3 to 4 times a week compared with once a day in the control group. This study, using a biopsychosocial approach in understanding sexual dysfunctions, is in contrast with previous, mainly uncontrolled, studies of epileptic patients that reported high frequencies of "hyposexuality" in males [18]. Furthermore, it has recently been demonstrated that there is not a difference in libido and sexual functioning between epileptic patients who were in a stable relationship and controls [19].

On the other hand, Morrell compared the genital blood flow whilst watching erotic videos in 8 men suffering from TLE with normal controls, concluding that sexual dysfunction in epileptic men may be due to physiologic disruptions in sexual arousal [12].

Reproductive dysfunctions are also common in men with epilepsy and, among married men, they are confined to those with onset before 10 years of age. Reduced fertility, including decreased sperm count, abnormal morphology or impaired motility, and hypogonadism with loss of male escutcheon, gynecomastia and testicular atrophy, has been described [20].

Aetiology

Despite sexual disorders are common in people with epilepsy, the etiology remains still unknown but it is likely to be multifactorial involving neurological, iatrogenic, endocrine psychiatric and psychosocial factors.

Neurological Factors

Recent advances in understanding the neurobiology of human sexual behavior have shown the pivotal role of the limbic system. Disruption of these cortical regions either by fixed lesions (stroke, neoplasms, brain injury) or by epileptiform discharges can predispose to sexual dysfunction. Amygdala is a deep temporo-mesial area with extensive connections with the arcuate and preoptic nuclei, which are involved in the regulation of gonadotropin release.

Indeed, many studies have found hyposexuality to be more common in patients with focal seizures, especially originating from the temporal lobe. Gastaut and Collomb were among the first to note this association [11], and other researchers have found that sexual disorders are more frequent in patients with PE, whether of temporal or extratemporal lobe origin, than in those with generalized epilepsy (GE). On the contrary, Fenick found similar rates of sexual dysfunction in patients with PE and GE [21]. Kuba *et al* showed a relatively high incidence (55%) of sexual disorders (especially impairment of sexual desire) and dissatisfaction with sexual intercourse and sex life in men with refractory focal epilepsy [22].

Interestingly, Hamed *et al* have recently found an unusual higher frequency of sexual dysfunction among epileptic men with generalized tonic-clonic convulsions. In this sample, the risk of sexual dysfunction was further increased by poor seizure control and the frequent association with mood and anxiety disorders [23]. Several studies have demonstrated laterality effects in patients with PE. In particular, LH pulse frequency has been shown to be greater in patients with right temporal epileptiform activity or left paroxysmal slowing. Moreover, Daniele *et al* documented reduction of libido and frequency of sexual intercourse to occur more frequently in men with right-sided TLE than left- sided [24].

Regarding age of onset and duration of epilepsy, Gastaut observed that all the patients with childhood-onset epilepsy developed hyposexuality, compared with onset after puberty, concluding that seizures might exert a marked disturbance on the development of sexual attitudes and behavior [12]. It has been reported that men with early-onset epilepsy were less likely to be merry and sexually active even if authors did not find a correlation between patient age or duration of epilepsy and sexual dysfunction [25].

Some studies reveal an association between severity of epilepsy and sexual disorders, and between improvement of sexual function and seizure control, attained either with anticonvulsivant medication, or following successful temporal lobectomy. Many of the studies documenting significant hyposexuality were in patients seen in tertiary referral centre or assessed for epilepsy surgery [13-18-26].

Endocrine Factors

Both seizures and antiepileptic drugs can affect the hypothalamic-pituitary-gonadal male axis causing changes in hormones and sexuality.

Normal testicular function is required for the expression of secondary sexual features, through the secretion of testosterone by the Leydig cells, and for fertility, through the production of production of spermatozoa. These functions depend on the stimulation of the pituitary gonadotropins LH and FSH, the release of which is controlled by hypothalamic GnRH. While LH stimulates testosterone production, FSH drives spermatozoa production by Sertoly cells, which also secrete inhibin B, the major feedback regulator of FSH secretion in men. It has been shown that epileptic discharges are associated with abnormal bioavailable serum testosterone and gonadotropin concentrations, altered LH response to GnRH stimulation, and increased serum PRL concentrations [27].

Studies have shown that seizures may produce transient surges in PRL, a hormone produced by the pituitary gland with a baseline levels surging during sleep and returning in daytime levels 60-90 minutes after waking [25]. Serum PRL has been reported to rise within 20 minutes in most patients with spontaneous generalized seizure, in 39-100% with complex partial seizures and only in up to 10% with simple partial seizures. Interestingly, PRL release tends to exhaust during status epilepticus. The rise in PRL occurs within five minutes of the seizure onset and may remain elevated for 1-hour post-ictally. Interictal levels tends to be normal even if some authors found mildly increased levels in drug free patients, possibly related to sub-clinical seizures. It is well known that hyperprolactinemia is associated with sexual dysfunction; thus a possible PRL involvement in hyposexuality, especially in right-sided epilepsy, can be postulated.

Nevertheless, Bauer et al. described 200 male patients, of whom 167 were receiving a single AED and 33 no treatment: sexual hormone levels did not differ, overall, in patients with ongoing seizures and those whose seizures were controlled suggesting that epilepsy may interfere with testicular function by means other than reduction of LH secretion caused by ictal or interictal discharges [28].

Moreover, Kuba *et al* found some specific hormonal changes related to various types of sexual dysfunction, not related to antiepileptics drugs (AEDs), i.e. an increase of FSH an SHBG, and a decrease of dehydroepiandrosterone sulfate (DHEAS) and free androgen index (FAI) [22].

Separating the direct effects of epilepsy vs medication has always been difficult because of the challenge of finding sufficient numbers of untreated epilepsy patients to serve as a control [29].

Anticonvulsivant Medication

In addition to the effect of epilepsy itself, AEDs seem to contribute to hormonal alterations associated with sexual dysfunction. It has been suggested that AEDs may have differential influence on the metabolism of sexual hormones and their binding proteins with secondary complications. Moreover, some AEDs may adversely affect normal reproductive cycling and sexual function through increasing serotoninergic transmission [30]. Enzyme-inducer AEDs, such as carbamazepine (CBZ), phenytoin (PHT) and phenobarbital (PB), elevate SHBG and reduce bioactive testosterone levels. Increased levels of E2, SHBG, FSH and DHEAS have been reported in men with erectile dysfunction, while a decrease of DHEAS is believed to be associated with loss of sexual desire.

Hergoz *et al* [31] found that men with partial seizures taking PHT have raised E2 levels. The author supposed that hepatic microsomial enzyme inducer AEDs could lower testosterone by promoting SHBG synthesis and by inducing aromatase, which converts testosterone in estradiol, the major inhibitor of LH secretion. Suppression of LH results in hypogonadotropic hypogonadism and chronically low testosterone to testicular failure and hypergonadotropic hypogonadism.

It has been suggested that PHT is associated with reduced sperm motility, semen volume, spermatozoa concentration and sperm count.

Valproate (VPA) is distinguished from other first-line AEDs in that it has enzyme-inhibiting effects. VPA has been implicated to have only minor effects on the hormonal system in men with epilepsy.

Indeed, while maintaining androgen levels, VPA seems to increase estrogens levels, perhaps by suppressing enzymatic metabolism of estradiol.

Recent studies in men with epilepsy have shown that both CBZ and VPA are associated with reduced sperm motility and increased frequency of morphologically abnormal sperm; only VPA was also associated with small testicular size [32, 33].

Oxcarbazepine (OXC), a ketoderivate of CBZ, has a different metabolic pathway in the liver since it is mainly metabolized by reduction, and does not appear to induce the oxidative P450-enzyme system to the same extent as CBZ. Thus, OXC has been suggested to be a safe AED with regard to endocrine and metabolic effect. However, there is evidence that OCX may also induce liver enzyme when used at higher dosage.

A recent study by Rattya et al have demonstrated that VPA may directly affect steroid synthesis and metabolism, while CBZ and OCX seem to have different reproductive effects in men with epilepsy whereas OCX does not appear to decrease the bioactivity of androgens and CBZ does [34].

Interestingly, it has been shown that more than 80% of patients with enzyme-inducing AED pretreatment experienced an improvement or did not complain about SD after switching to OCX [35]. On the other hand, a recent clinical study has demonstrated an association between OCX and morphologically abnormal sperm [32].

Non enzyme-inducing AEDs such as lamotrigine (LTG) may offer a distinct and important advantage in the area of reproductive endocrine function in men as they do not alter sexual hormone. Indeed, it has been demonstrated that LTG use is associated with sexual function, levels of bioactive testosterone and gonadal efficiency values that are comparable to those of normal controls and superior to those found with CBZ and PHT [36].

Nevertheless, it has been recently demonstrated that even the new AEDs can determine sexual dysfunction through complex and poorly understood mechanisms.

TPM, a drug approved for the treatment of both partial and generalized epilepsies and for migraine prophylaxis, has been reported to cause erectile dysfunction (ED) in few cases [37-38].

Calabrò *et al* have postulated that TPM induced-ED might be due to a blockage of AMPA receptors with an inhibition of the glutamatergic pathway, whereas glutamate is considered a candidate neurotransmitter of reflexive erection [38].

Pregabalin (PBG), a new AED structurally related to gabapentin (GBP), modulates the release of several neurotransmitters through its binding to voltage-dependent calcium channels and it is commonly used as adjunctive therapy for partial epilepsy. ED associated with PBG has been recently described in a case series, but pathophysiological mechanisms remains still unclear [39].

Reversible ED induced by zonisamide (ZNS) has been described so far only in a patient affected by brain tumor [40]. ZNS is a sulfonamide derivate and shares with TPM some common action mechanisms such as blockade of voltage-dependent sodium channels and inhibition of carbonic anhydrase. It has been suggested that ZNS-related dysfunction could be due to an impairment of the complex interplay between the serotoninergic and nitrergic pathways [41].

Although OCX and LTG are thought to ameliorate sexual function in pre-treated epileptic men, some sexual side effects has been reported. In particular, hypersexuality has been related to LTG-treatment in two patients with epilepsy [42]; anorgasmia has been recently described as a dose-dependent and reversible side effect of OCX [43].

Levetiracetam (LVT) is a relatively new, broad-spectrum AED that has seen extensive use during recent years. It has recently reported that LEV treatment apparently has no drug specific sexual or endocrine side effects in young-adult epileptic men [44].

The hormonal effect of the other new AEDs (felbamate, gabapentin, tiagabine, tipiramate, vigabatrin) has not been studied, to our knowledge, in men with epilepsy.

Psychiatric Diseases

Several studies have found a high prevalence of psychiatric comorbidity in patients affected by epilepsy, especially in those with temporal lobe epilepsy [45]. It is well known

that psychiatric disorders, both neurotic and psychotic, are often associated with hyposexuality. Indeed reduced libido, erectile dysfunction and anorgasmia are common features of depression or anxiety states. Moreover, medication used to treat psychiatric disorders, including neuroleptics and antidepressants, may also impair sexual function. The actual incidence and prevalence of depression in epilepsy remains uncertain, despite the numerous research studies addressing this issue. However its incidence is higher than a matched population of healthy controls with a range of 11% to around 62%. TLE is considered a possible risk factor for depression because it subsumes the limbic system which is involved in affect and mood regulation. Other important risk factors for depression are considered neurochemical factors (i.e. depletion of NE, 5HT, and DA with consequent up regulation of the synaptic receptors), psychological factors (i.e. increased perceived stigma, amount of social support, poor vocational adjustment, external locus of control, increased stressful life events, less adequate financial status), and iatrogenic factors. Interestingly, epileptic patients that meet criteria for Major Depression, presented atypical features with more paranoia and psychotic symptoms.

Psychosocial Factors

The fear of rejection and the heightened sensitivity toward being the target of stigmatization by the general population are unfortunate widespread problems that patients with epilepsy must face. Such problems undoubtedly may contribute to patient feeling sexual inadequacy and explained the inevitability of anticipatory anxiety regarding sexual intercourse. Besides, a fear of having seizures in the midst of sexual intercourse can lead to avoidance of sexual activity, resulting in partner's feeling of rejection, guilt and, eventually, a distancing between the sexual partners.

Diagnostic Workup

The initial evaluation of epileptic patients with sexual dysfunction, especially ED, should be done with awareness for the multifactorial etiologies.

It is likely that epilepsy itself, antiepileptic drugs, and psychosocial factors all play a role.

First of all, personal, sexual and relationship history is necessary to understand patient's complaints. Life stressors should be taken into account as contributing factors to sexual disturbance. Furthermore a psychological screening for depression and anxiety disorders should be performed. Medication history plays an important role: beside the antiepileptic therapy, there are many other possible drugs, i.e. antidepressants, neuroleptics, sedatives, β-blockers, diuretics, leading to sexual side effects. General, neurological and uro-genital examination is necessary to point out medical comorbidities. ED can be the first clinical sign of an unknown and untreated cardiovascular disease, so an accurate evaluation of the heart and of the main arteries should be done.

Then, a full endocrine and metabolic work-up should be performed. Serum levels of testosterone, DEAHS, SHBG, estradiol, LH, FSH, and PRL, and thyroidal function should be evaluated.

The nocturnal tumescence measurement can help distinguish between organic and psychogenic ED so that, in the cases of a suspected organic disease further and more specific investigation (pudendal PESS, Doppler, etc) should be performed.

Although sexual dysfunction is common in epileptic patients, its quantification is limited by the paucity of validated, user-friendly scales. Sexual functioning measured by using the Arizona Sexual Experience Scale (ASEX), a brief five-item scale designed to assess the core elements of sexual function: drive, arousal, penile erection/vaginal lubrification, ability to reach orgasm, and satisfaction with orgasm is often used. The IIEF-score (International Index of Erectile Function) and the erection hardness score help to standardize ED and are useful to show success during therapy.

Treatment

Once the etiology of sexual dysfunction is determined, proper treatment strategies should follow.

If sexual dysfunction had clearly an onset coincident with starting an antiseizure medication, changing the medication should be considered. Concomitant psychiatric comorbidities should be treated using, when possible, drugs with lower sexual side effects.

If testosterone levels are low in patients experiencing decreased libido and potency, testosterone replacement should be considered with the goal of restoring normal concentrations. Several investigators have observed some improvement in male sexual dysfunction after the administration of testosterone. Hergoz et al [46] reported that although amelioration of sexual dysfunction was noted, the response was only modest, possibly because of AED-induced aromatization of testosterone to estradiol. Therefore, the authors noted that men treated with the adjunctive use of an aromatase inhibitor had a greater improvement than those who received testosterone alone.

The use of PDE-5 inhibitors to treat ED in patients taking AEDs may also prove to be a reasonable approach, but no prospective trials of the drugs' efficacy or safety have been conducted in this patient population. Interestingly, it is of some concern that generalized tonic-clonic seizures have been reported in patients taking sildenafil who had no history of epilepsy [47]. Nevertheless, sildenafil can be used safely in epilepsy patients for restoring sexual performance. It is used intermittently as a single dose; therefore, drug interactions are not expected even if clearance of sildenafil may be reduced by inhibitors of the cytochrome P450.

Further therapy options belong to urologist's armamentarium, i.e. the use of an elastic constricting band or of a vacuum device to achieve and maintain erection. More invasive, but effective, regimens are the intraurethral application of prostaglandin (PG) E1, so called MUSE, or the intracavernosal self-injection of papaverine, phentolamine and PGE1.

Conclusion

Sexual function is an important marker of well-being and since patients with epilepsy may not spontaneously complain of dysfunction, physicians and other health care workers

should always discuss it when interviewing patients. Seizures, hormones and sexuality have a complex relationship and much is still not understood about their interaction. In order to more fully understand the etiology of sexual dysfunction in epilepsy, large and prospective studies have to be performed in selective patient population. These specific studies must attempt to determine the effects of epilepsy per se and the individual treatments on sexual function, taking into account psychosocial factors.

References

[1] Baker GA, Brooks J, Buck D, Jacoby A. The stigma of epilepsy: a European perspective. *Epilepsia.* 2000; 41:98-104.

[2] Bishop M, Allen CA. The impact of epilepsy on quality of life: a qualitative analysis. *Epilepsy Behav*. 2003;4:226-33

[3] Jacoby A, Snape D, Baker GA Determinants of quality of life in people with epilepsy. *Neurol Clin*. 2009; 27:843-63.

[4] Guekht AB, Mitrokhina TV, Lebedeva AV, Dzugaeva FK, Milchakova LE, Lokshina OB, Feygina AA, Gusev EI. Factors influencing on quality of life in people with epilepsy. *Seizure*. 2007;16:128-33.

[5] Leidy NK, Elixhauser A, Vickrey B, Means E, Willian MK Seizure frequency and the health-related quality of life of adults with epilepsy. *Neurology.* 1999 ; 53:162-6

[6] Leutmezer F, Serles W, Bacher J, Gröppel G, Pataraia E, Aull S, Olbrich A, Czech T, Baumgartner C.Genital automatisms in complex partial seizures. *Neurology.* 1999; 52:1188-91.

[7] Aull-Watschinger S, Pataraia E, Baumgartner C. Sexual auras: predominance of epileptic activity within the mesial temporal lobe. *Epilepsy Behav*. 2008; 12:124-7.

[8] Mascia A, Di Gennaro G, Esposito V, Grammaldo LG, Meldolesi GN, Giampà T, Sebastiano F, Falco C, Onorati P, Manfredi M, Cantore G, Quarato PP.Genital and sexual manifestations in drug-resistant partial epilepsy. *Seizure*. 2005;14:133-8.

[9] Ozkara C, Ozdemir S, Yilmaz A, Uzan M, Yeni N, Ozmen M. Orgasm-induced seizures: a study of six patients. *Epilepsia.* 2006; 47:2193-7.

[10] Toone, B.K. Sexual disorders in Epilepsy. In: Recent Advances in Epilepsy. Vol 3. (Eds TA Pedley and BS Meldrum). Edinburgh, Churchill Livingstone, 1986: 233-259.

[11] Gastaut H and Collomb H. Etude du comportement sexual chez les epileptiques psychomotors. *Annales Medico-Psychologiques*. 1954; 112: 657-659.

[12] Morrell MJ, Sperling MR, Stecker M, Dichter MA. Sexual dysfunction in partial epilepsy: a deficit in physiologic sexual arousal. *Neurology*. 1994;44:243-7.

[13] Taylor DC. Sexual behavior and temporal lobe epilepsy. Arch Neurol 1969;21:510-6

[14] Toone BK, Edeh J, Nanjee MN, Wheeler M. Hyposexuality and epilepsy: a community survey of hormonal and behavioural changes in male epileptics. *Psychol Med*. 1989; 19:937-43

[15] Smaldone M, Sukkarieh T, Reda A, Khan A. Epilepsy and erectile dysfunction: a review. *Seizure.* 2004;13: 453-9.

[16] Spector IP, Carey MP Incidence and prevalence of the sexual dysfunctions: a critical review of the empirical literature. *Arch Sex Behav*. 1990; 19:389-408.

[17] Nikoobakht M, Motamedi M, Orandi A, Meysamie A, Emamzadeh A. Sexual dysfunction in epileptic men. *Urol J*. 2007;4:111-7.

[18] Jensen P, Jensen SB, Sørensen PS, Bjerre BD, Rizzi DA, Sørensen AS, Klysner R, Brinch K, Jespersen B, Nielsen H Sexual dysfunction in male and female patients with epilepsy: a study of 86 outpatients. *Arch Sex Behav.* 1990; 19:1-14.

[19] Duncan S, Blacklaw J, Beastall GH, Brodie MJ.Antiepileptic drug therapy and sexual function in men with epilepsy. *Epilepsia.* 1999; 40:197-204.

[20] Herzog AG. Disorders of reproduction in patients with epilepsy: primary neurological mechanisms. *Seizure*. 2008; 17: 101-10.

[21] Fenwick PB, Toone BK, Wheeler MJ, Nanjee MN, Grant R, Brown D. Sexual behaviour in a centre for epilepsy. *Acta Neurol Scand*. 1985;71:428-35

[22] Kuba R, Pohanka M, Zákopcan J, Novotná I, Rektor I. Sexual dysfunctions and blood hormonal profile in men with focal epilepsy. *Epilepsia.* 2006 ;47:2135-40

[23] Hamed S, Mohamed K, El-Taher A, Hamed E, Omar H. The sexual and reproductive health in men with generalized epilepsy: a multidisciplinary evaluation. *Int J Impot Res.* 2006;18: 287-95.

[24] Daniele A, Azzoni A, Bizzi A, Rossi A, Gainotti G, Mazza S. Sexual behavior and hemispheric laterality of the focus in patients with temporal lobe epilepsy. *Biol Psychiatry* 1997;42:617-24.

[25] Lambert MV. Seizures, hormones and sexuality. *Seizure*. 2001; 10: 319-40.

[26] Hierons R and Saunders M. Impotence in patients with temporal lobe lesions. *Lancet*. 1966; 2:761- 764.

[27] Montouris G, Morris GL 3rd. Reproductive and sexual dysfunction in men with epilepsy. *Epilepsy Behav.* 2005; 7 Suppl 2:S7-14.

[28] Bauer J, Blumenthal S, Reuber M, Stoffel-Wagner B. Epilepsy syndrome, focus location, and treatment choice affect testicular function in men with epilepsy. *Neurology.* 2004; 62:243-6.

[29] Gates JR Epilepsy versus antiepileptic drugs and gonadal function in men. *Neurology.* 2004; 62:174-5.

[30] Hamed SA Neuroendocrine hormonal conditions in epilepsy: relationship to reproductive and sexual functions. *Neurologist.* 2008; 14:157-69.

[31] Heroz AG, Levesque LA, Drislane FW, Ronthal M, Schomer DL. Phenytoin-induced elevation of serum estradiol and reproductive dysfunction in men with epilepsy. *Epilepsia.* 1991;32: 550-3.

[32] Isojärvi JI, Löfgren E, Juntunen KS, Pakarinen AJ, Päivänsalo M, Rautakorpi I, Tuomivaara L. Effect of epilepsy and antiepileptic drugs on male reproductive health. *Neurology.* 2004;62(2):247-53

[33] Isojärvi J.Disorders of reproduction in patients with epilepsy: antiepileptic drug related mechanisms. *Seizure.* 2008;17: 111-9.

[34] Rättyä J, Turkka J, Pakarinen AJ, Knip M, Kotila MA, Lukkarinen O, Myllylä VV, Isojärvi JI.Reproductive effects of valproate, carbamazepine, and oxcarbazepine in men with epilepsy. *Neurology.* 2001;56:31-6

[35] Luef G, Krämer G, Stefan H.Oxcarbazepine treatment in male epilepsy patients improves pre-existing sexual dysfunction. *Acta Neurol Scand*. 2009;119: 94-9.

[36] Herzog AG, Drislane FW, Schomer DL, Pennell PB, Bromfield EB, Dworetzky BA, Farina EL, Frye CA. Differential effects of antiepileptic drugs on sexual function and hormones in men with epilepsy. *Neurology*. 2005;65:1016-20

[37] Holtkamp M, Weissinger F, Meierkord H. Erectile dysfunction with topiramate. *Epilepsia*. 2005;46:166-7

[38] Calabrò RS, Bramanti P, Italiano D, Ferlazzo E. Topiramate-induced erectile dysfunction. *Epilepsy Behav*. 2009;14:560.

[39] Hitiris N, Barrett JA, Brodie MJ.Erectile dysfunction associated with pregabalin add-on treatment in patients with partial seizures: five case reports. *Epilepsy Behav*. 2006;8:418-21

[40] Maschio M, Saveriano F, Dinapoli L, Jandolo B. Reversible Erectile Dysfunction in a Patient with Brain Tumor-Related Epilepsy in Therapy with Zonisamide in Add-On. *J Sex Med*. 2009 Jun 29.

[41] Calabrò RS, Italiano D, Bramanti P, Ferlazzo E. Zonisamide-related erectile dysfunction. *J Sex Med*. 2010 Jan 25.

[42] Grabowska-Grzyb A, Nagańska E, Wolańczyk T. Hypersexuality in two patients with epilepsy treated with lamotrigine. *Epilepsy Behav*. 2006;8:663-5.

[43] Calabrò RS, Ferlazzo E , Italiano D, Bramanti P Dose-dependent oxarcarbazepine-induced anorgasmia. *Epilepsy Behav*. 2010;17:287-8.

[44] Svalheim S, Taubøll E, Luef G, Lossius A, Rauchenzauner M, Sandvand F, Bertelsen M, Mørkrid L, Gjerstad L. Differential effects of levetiracetam, carbamazepine, and lamotrigine on reproductive endocrine function in adults. *Epilepsy Behav*. 2009;16:281-7.

[45] Alan B Ettinger and Andres M Kanners, editors. Psychiatric issues in Epilepsy: a practical guide to diagnosis and treatment. Lippincott William and Wilkins, USA. 2001.

[46] Herzog AG, Klein P, Jacobs AR.Testosterone versus testosterone and testolactone in treating reproductive and sexual dysfunction in men with epilepsy and hypogonadism. *Neurology*. 1998;50:782-4.

[47] Gilad R, Lampl Y, Eshel Y, Sadeh M.Tonic-clonic seizures in patients taking sildenafil. *BMJ*. 2002;325:869.

In: Male Sexual Dysfunctions in Neurological Diseases… ISBN 978-1-61761-855-0
Editor: Calabrò Rocco Salvatore

Chapter 5

Sexuality after Stroke

Rocco Salvatore Calabrò and Giuseppe Gervasi
IRCCS Centro Neurolesi "Bonino-Pulejo",
Messina, Italy

Abstract

Stroke is the leading causes of death and disability throughout the world. Although physical and cognitive impairments after stroke have been well studied, little information is known about one of the crucial aspect of the quality of life of stroke patients, namely sexual functioning and satisfaction. Post-stroke sexual dysfunctions seem to be very common; in men affected by stroke, a decline in libido and poor or tailed erection and ejaculation are frequently observed.

Sexual disorders after stroke are thought to be due to multiple etiologies, including both organic (i.e lesion localization, premorbid medical conditions, medications) and psychosocial (i.e fear of recurrences, loss of self-esteem, role changes, anxiety and depression). Thus, exploration in sexual dysfunctions and sexual counselling by trained professionals should be part of stroke rehabilitation.

Introduction

Stroke, also known as cerebrovascular accident (CVA) or "brain attack", is a syndrome caused by a focal disruption in the cerebral blood flow due to occlusion of a blood vessel (ischemic stroke) or rupture of a blood vessel (hemorrhagic stroke). The interruption in blood flow deprives the brain of nutrients and oxygen, resulting in injury to cells in the affected vascular territory of the brain. Ischemic strokes are more common than hemorrhagic ones (80% vs 20%).

When brain cells die, function of the body parts they control is impaired or lost, causing paralysis, speech and sensory problems, memory and reasoning deficits, coma, and possibly death.

Classification and etiopathogenesis of both ischemic and hemorrhagic stroke are shown in tables 1 and 2

Table 1. Etiopathogenesis of ischemic stroke

Causes	
Common	Atherosclerosis Small vessels diseases Cardioembolism/transcardial embolism
Uncommon	Emathological disorders Migraine stroke Oral contraceptive/estrogen Non estro-progestinic drugs
Unusual	Primary vasculitis • Giant cells arteritis • Takayasu's arteritis • Systemic Lupus Erythematosus • Sneddon syndrome • Systemic necrotizing arteritis • Nodal Osteoarthritis • Churg-Strauss Syndrome • Wegener syndrome • Rheumatoid Arthritis • Sjögren Syndrome • Behçet diseas
	• Relapsing polychondritis • Sclerodermia • Sarcoidosis • Bürger's Diseases • Central Nervous System arteritis Secondary vasculitis • Infection (Viral, bacterial) • Drugs • Beam radiation • Celiachia's disease • Chronic inflammatory bowel diseases Inborn malformation • Fibromuscular dysplasia • Carotid Kinking and coiling • Basilar artery ectasia • Elhers-Danlos syndrome • Elastic Pseudoxantoma • Marfan's Syndrome • Artero-venous malformation Injured vasculopathies such as carotid dissection Other cause • Snake poison • Fatty/gas embolia • Cerebral autosomal Dominant Arteriopathy with Subcortical Infarcts and Leucoencephalopathy (CADASIL) Fabry's disease

Table 2. Etiopathogenesis of Hemorrhagic stroke

Side	Causes
Intraparenchymal Hemorrage	Hypertension Diabetes Mellitus Brain trauma Internal Carotid artery dissection Eclampsia Reperfusion injury Rupture of aneurysm or artero-venous malformation Arteriopathies such as Moya-Moya, Takayasu's Syndrome and Fibromuscular Dysplasia Altered hemostasis (thrombolysis, anticoagulation) Hemorrhagic necrosis (tumor) Venous outflow obstruction (cerebral sinus venous thrombosis)
Extraparenchymal Hemorrage	Subarachnoid hemorrhage – Brain trauma – Rupture of aneurysm – Rupture of artero-venous malformation – Artery dissection Extradural hemorrhage – Brain trauma – Artery dissection – Dural artero-venous fistulas

Epidemiology of Stroke

Stroke could soon be the most common cause of death worldwide. Indeed, it is currently the second leading cause of death in the Western world, ranking after heart disease and before cancer, and causes 10% of deaths worldwide. Geographic disparities in stroke incidence have been observed, including the existence of a "stroke belt" in the southeastern United States, but causes of these disparities have not been explained. The incidence of stroke increases exponentially from 30 years of age, and etiology varies by age. Advanced age is one of the most significant stroke risk factors. Ninety-five percent of strokes occur in people age 45 and older, and two-thirds of strokes occur in those over the age of 65. However, stroke can occur at any age, including in fetuses.

Quality of Life in Stroke Survivors

The most difficult aspect of having a stroke is living with the disability caused by this condition. Stroke is associated with high morbidity rates, meaning that many patients experience both physical and mental disability following the event. In fact, stroke morbidity is the leading cause of decreased independence and lowered quality of life (QoL) among adults. Interestingly, coping strategies are powerful determinant of QoL, but only more than 5 months after discharge; before this time QoL is mainly determined by general functioning [1-2]. Despite the enormous personal and societal impact of stroke, the best method for measuring stroke outcome is not clear, even if assessment of stroke impact has been standardized. The National Institute of Health Stroke Scale (NIHSS) contains 13 items and measures severity of impairment in consciousness, orientation, gaze, motor function, sensation, language, speech and inattention, while the modified Rankin scale measures handicap or death on a scale of 1-6.

Nevertheless, some commonly used stroke outcome measures, such as the Barthel Index, a measure of disability in 10 functional items, and the Short Form 36 (SF-36), for example, have no assessment of language. Consequently, patients with severe aphasia may have a normal score on these measures and therefore be classified as having "good" outcome for purposes of analysis of drug efficacy. Other domains often neglected in stroke outcome assessments are cognitive, psychological, and social function [3].

Sexuality is an integrant and important part of QoL and patient affected by neurological disability, especially if young, should also be investigated and treated for sexual disorders. Indeed, it is common knowledge that the impact of sexual dysfunctions on patients with recent stroke is great; however even though they suffer from sexual impairment, patients usually do not ask for counselling, and, moreover, they are not commonly investigated for this issue by physicians.

Aim of this chapter is to evaluate the burden of stroke on sexual function taking into account the complex interaction between neurological, psychological and relational factors.

Sexual Dysfunction after Stroke

Sexual function relies on a complex network of peripheral and central pathways involving the participation of autonomic and somatic nerves and the integration of numerous spinal and supraspinal sites in the central nervous system (CNS), with the hypothalamic and limbic regions playing a pivotal role (4).

Neurological diseases have long been recognized as causing sexual dysfunction through an altered processing of sexual stimuli to preclude arousal, to decrease or increase desire, or to curtail genital engorgement [5].

Various studies have shown a significant decrease in sexual satisfaction after CVA [6-11]. In men affected by stroke, a decline in libido and poor or tailed erection and ejaculation are frequently observed. Indeed, the reported prevalence of post-stroke diminished libido varies from 17% to 42%. Korpelainen et al. [11] showed a significant decline in libido, sexual arousal and satisfaction with sexual life in both male and female stroke patients, but the frequency of patients who ceased having sexual intercourse was lower (28% at 2 months and 14% at 6 months) than in the previous studies. The same authors demonstrated that sexual

dysfunction was strictly related to the presence of sensory hemisyndrome, in agreement with Sjogren et al [12], who found that changes in the frequency of intercourse were related to the degree of cutaneous sensibility impairments and levels of independence in activities of daily living, but not with the degree of motor impairment. Tactile stimulations are extremely important in sexual arousal and orgasm during foreplay and intercourse. Therefore, it is obvious that sensory hemisyndrome may be related to problems with erection, ejaculation and orgasm resulting in impaired libido and quality of life.

Interestingly, a significant decline in coital frequency, sexual satisfaction, libido, sexual arousal and orgasm has been demonstrated among stable stroke patients with mild or no disability [13].

Some male patients experience temporary sexual problems, usually regaining erectile function after around seven weeks following the stroke, whereas others do not seem to recover sexual intercourse, and/or show a worsening in time.

The cause of sexual dysfunction is often multifactorial with a complex interplay between psychological and organic factors. In fact, sexual problems seem to be related to various factors, like the general attitude toward sexuality, an incipient depression with anxiety after the CVA or prior medical conditions such as hypertension, diabetes mellitus, or the use of specific drugs.

Some authors have postulated a relationship between the location of the lesion and sexual change, since sexual disorders appear to be more frequent when the right hemisphere is involved [14-15]. Coslett et al. reported in a study of unilateral stroke patients that those with a stroke lesion in the right cerebral hemisphere experienced a significant decrease in sexual desire and in the frequency of intercourse. Indeed, libido and ability to achieve erection may require activation of specific limbic and cortical structures, and the right hemisphere seems to be dominant for attention/activation functions and in processing emotions. Moreover, the right hemisphere dominance for male sexual activity may be related to the specific control of hypothalamus-pituitary axis, as suggested by the observation of altered sexual behaviors in patients with right temporal lobe epilepsy [16].

Nevertheless, to date, a few studies have attempted to determine the correlations between the sexual function of stroke patients and the locations of their lesions. Jun et al [17] have shown that patients with multiple brain lesions had a significant decrease of erectile function compared with those with one lesion. In particular, a decrement of sexual desire was associated with a stroke lesion on the left basal ganglia; patients with lesions in the right cerebellum experienced significant ejaculatory disorders; and patients with lesion in the right pons were associated with a decrease in the IIEF-5 score. Jeon et al [18] demonstrated that patients with CVA lesions of the thalamus showed more erectile dysfunction than the patients with CVA lesions of any other areas. This would point out the possible role of thalamus in human penile erection supporting those data from preclinical studies that suggested how thalamic caudal and lateral intralaminar nuclei are involving in processing the sexual outflow from the spinothalamic pathway towards the preoptic area, amygdala, temporal lobe, and the frontal cortex.

On the contrary, few authors did not find a significant correlation between decline of sexual intercourse after stroke and injured hemisphere [9], whereas few findings reported a greater incidence of sexual disorders after left-hemisphere [19]. However, it should be taken into account that depression often accompanies left rather than right hemisphere damage and depression may certainly lead to sexual impairment.

Interestingly, behavioral alterations after stroke may play a role in the aetiology of sexual changes. Hypersexuality has been related to temporal lobe lesions, history of poststroke seizures and antidepressant activity [20]. A case of hypersexuality following bilateral thalamic infarction has been recently described, showing how frontal-subcortical circuits may have a pivotal role in the pathogenesis of this sexual disorder [21]. Indeed, it seems that lacunar strokes that affect the frontolimbic connections have special propensity to cause hypersexuality: profoundly disinhibited sexuality and hemiballism has been reported after the infarction of the subthalamic nucleus [22].

Jawad et al reported on a case of altered sexual orientation (homosexual to heterosexual) following an infarct in the left middle cerebral artery region; thus, the authors recommended addressing this issue, in addition to other possible behavioral changes, while assessing patients after a brain injury [23]. Stroke that affects the right-medial frontal cortex and the anterior portion of the corpus callosum is one of the possible vascular causes of the so-called alien hand syndrome, which can cause the perception that one hand belongs to someone else, and can induce purposeful involuntary movements, even self-masturbatory movements on the genitalia [24].

Emotional incontinence (EI), characterized by excessive and/or inappropriate laughing/crying, has been occasionally reported after unilateral stroke. Chi-Kwon and Kim have investigated, for the first time, both post-stroke EI and sexual activity changes in the subacute as well as the chronic stage of stroke; according to the authors, the presence of EI is a factor related to decreased poststroke sexual activity suggesting a possible alteration of an identical neurotransmitter system [25]. Moreover, a stroke may impair the ability to correctly interpret other's emotions, to express the emotions of love and joy, and to notice, interpret and express the subtle emotional cues essential to romance and love.

Physical impairment could have an important role in the etiology of long-term sexual problems. In common with severe brain trauma, the effects of a devastating stroke may influence body positioning and movement and challenge the ability to embrace and stimulate the partner during sexual intercourse. Obvious drawbacks are drooling, bladder and bowel incontinence, and other potentially unattractive behaviors. Indeed, facial dropping, speech and memory problems, hemiparesis, difficulty eating, and incontinence all may contribute to feeling less attractive with a consequent loss of desire and important reduction in sexual intercourse [26]. Right-middle cerebral artery strokes have the potential to produce not only hemianesthesia but also perceptual neglect (i.e. the inability to interpret the left side of the environment), both of which might interfere with erotic sensations.

The role of previous medical conditions in the pathogenesis of post-stroke sexual dysfunction is still under debate. Because stroke tends to occur with increasing age, changes in sexual response with aging have to be taken into account when dealing with survivors of stroke. Indeed, in men it takes longer and more direct stimulation to achieve an erection; erections are not as hard and do not last long; orgasm may be not reached with every sexual encounter.

Risk factors for having a stroke, beyond older age, include diabetes mellitus, hypertension, dyslipidemia and hyperhomocysteinemia, heart disease, peripheral vascular disease, and chronic lung disease. Although it is unlikely that people with stroke have all of these premorbid conditions, they are likely to have at least one. The atherosclerosis, that causes hypertension, heart disease, and stroke, may also reduce genital circulation and cause ED. However, the longer one has the disease and the more severe the symptoms are, and the

more likely the sexual problems are. Beside the direct impact of the disease on the sexual function, many drugs used in these diseases, such as antihypertensives, particularly beta blockers, may lead to sexual problems.

Bener et al. [27] have demonstrated that the most important co-morbid factors for ED in stroke patients were diabetes, hypertension, and hypercholesterolemia, and the risk factors were smoking and obesity.

Mood disorders, such as depression, anxiety, and post-traumatic stress syndrome, are often observed after a stroke, and therefore post-stroke depression commonly results in sexual dysfunction and conversely. Changes in mood seem to be related to dependence to activities in daily living (ADL) and to the severity of neurological deficits. It is not a coincidence that people with more severe physical impairments experience emotional disorders and decreased sexual intercourse more frequently than people with mild impairment. Indeed, Kimura et al reported that patients with sexual dysfunction after stroke had more frequent and severe depressive disorder or more impaired ADL compared with patients without sexual dysfunction [28]. Depression and fear of a recurrent stroke are examples of psychological factors influencing sexual function and, in particular, sexual desire, but low self esteem, partner refusal, loss of work, etc are other important issues to take into account. The dual-control model of male sexual responsiveness, developed to explain psychogenic erectile dysfunction, assumes that individuals vary in their propensity for inhibition and excitation [29] and that these propensities can be regarded as personality traits specifically related to sexuality.

Duits et al, for the first time, attempted to identify the relevance of sexual responsiveness to sexual function in male stroke patients [30] using the Sexual Inhibition/Sexual Excitation Scale (SIS/SES). This questionnaire includes 45 items exploring the propensity for sexual excitation (SES), the propensity for sexual inhibition because of the threat of performance failure (SIS1) - this fear is more intrinsic and related to inhibitory tone with a good response to pharmacological therapy- , and the propensity for sexual inhibition because of the threat of performance consequences (SIS2) - this fear is related to the perception of an external threat in a specific situation, such as the risk of catching a sexually transmitted disease or, in the case of stroke patients, the fear of a recurrent stroke. The authors found significant and negative relationships between SIS1 and both orgasmic and sexual desire whereas SIS2, anxiety and depression were not related to any of sexual variables; SES was instead significantly but positively associated to sexual desire.

There is general agreement that a lack of nocturnal penile erections indicates an organic etiology for impotence. In Korpelainen et al.'s series [11], 45% of the male patients showed penile erections, 55% showed impaired post-stroke penile erections, and none of the patients had a complete absence of nocturnal erections. Interestingly, 28% of the patients at 2 months and 14% at 6 months reported they had stopped having sexual intercourse, although their nocturnal erections still exist. Therefore, the authors supposed that both psychological and organic factors (i.e lesions of the autonomic and limbic nervous systems) may determine the form and quality of the sexual life of stroke patients.

The role of psychological factors is further confirmed by the observation that sexual disorders are reported not only by the patients, but also by their partners. The illness is often experienced as a critical event in life and the impact of stroke on the psychological health of caregivers is relevant. A higher level of emotional disorders among care-givers, especially in stroke patients' spouses, as compared with control, has been demonstrated [31]. Nevertheless,

little information is available about the consequences of stroke on sexual behavior and attitudes of the stroke patients' spouses, although they are very important in terms of stroke survivors' well-being. Previous studies [32-33] suggest that spouses experience negative changes in the quality of their sexual life similar to those of stroke patients, but there is a lack of detailed information regarding the changes in their sexual life. Korpelainen et al (10) revealed a significant decline in libido, coital frequency, sexual arousal, and satisfaction with sexual disorders significantly associated with various psychological factors, such as general attitude towards sexuality, fear of stroke recurrences and ability to discuss sexuality.

In addition to comorbidity, neurological and psychological factors, CNS driven alterations of the control of the autonomic system may also contribute to sexual impairments in stroke patients. Indeed, poststroke sympathetic hyper-function and/or parasympathetic hypo-function can determine abnormalities in heart response, pressure regulation, sudomotor and vasomotor regulatory systems. In this context, bladder and bowel dysfunction and impotence may be related to autonomic failure following stroke. Experimental and human studies suggest that the insular cortex, especially the right insula, is the most important cortical area controlling both sympathetically and parasympathetically mediated cardiovascular regulation thanks to its connection with other autonomic regulatory areas located in the subcortical limbic and forebrain regions [34]. Penile erection and ejaculation requires interplay of smooth and skeletal fibers, glandular and endothelial cells, controlled by the autonomic nervous system. As a result of this, autonomic pathways might constitute privileged targets for pharmacological treatment of poststroke sexual dysfunctions. Indeed, drugs focusing on the imbalance between sympathetic and parasympathetic systems may have important implications not just to reduce the risk of adverse cardiovascular events in the acute phase but also to improve the QoL in stroke survivors.

Aphasia and Sexuality. As we have previously underlined, changes in sexuality have attracted during the past decades the interest of researchers, but studies rarely included aphasic subjects because of the extreme difficulty to interview them. A pilot study by Lemieux et al. [35] showed a reduced frequency of sexual intercourse and an increasing in other sexual activities in their aphasic patients. Interestingly, patients reported it was harder to verbally initiate and talk about desire of sex, while their spouses evidenced that the aphasic partner was no longer able to express their feelings or engage in sexually intimate conversation. Thus, it is authors' opinion that aphasia affects sexuality differently than for other stroke patients and that their couples need discussing sexuality with their physicians.

Sexuality of stroke survivors is commonly affected by motor, sensory and autonomic dysfunction, but for people with aphasia sexual dysfunction is often more related to their communication disorder, since adequate communication skills are essential for forming and maintaining social and sexual relationships. Aphasia also represents a formidable barrier to talking about sexuality with health care professionals, especially when he is mute on this issue. Neglect of sexuality by health care workers denies access to assessment, counselling and treatment services, particularly in this scenario, wherein aphasic people lack the words to initiate these discussions themselves.

Stroke during sexual intercourse. The association between the various risk factors and stroke are well established, but very little is known about factors that may precipitate acute stroke. Negative emotions, anger, sudden changes in body posture in response to a startling event, and all Valsalva-provoking activities in the presence of a patent foramen ovale (PFO), i.e lifting a heavy weight, straining a stool, laughing, coughing, and trumpet or horn playing,

appear to be independent triggers for ischemic stroke [36-37]. Sexual intercourse has been described in few cases as an unusual trigger of stroke. Becker et al reported 4 patients who had stroke during sexual intercourse; all had echocardiographic evidence of a PFO and no obvious explanation for their strokes, making paradoxical embolism plausible. If PFO predispose to stroke, then it is assumed that venous clots may pass in the arterial circulation at the level of the atria. Since deep venous thrombosis has been rarely documented in patients with PFO and cryptogenic stroke, emerging evidence suggests that trombophilias are more prevalent in these individuals. During Valsalva maneuver, there is an increase in intrathoracic, central venous and right atrial pressure; if the right pressure exceeds the left one, a right-to-left shunt may occur through the PFO. The physiologic changes during coital activity, i.e heart rate and blood pressure increasing, are likely similar to those seen during Valsalva maneuver and thus could predispose individuals to paradoxical embolization.

The occurrence of acute stroke immediately after intercourse has been also attributable to vasospasm, cerebral hemorrhage or subarachnoid hemorrhage. Nonetheless, the only epidemiologic study which examined the relation between frequency of sexual intercourse and risk of ischemic stroke failed to demonstrate this correlation reassuring for the public who might reasonably believe that sexual activities can cause strokes [38].

Conclusion

Since the number of people who survive stroke and live with its consequences is increasing, there is a need for a better management of stroke related problems, including sexual dysfunction, providing the patients and their caregivers' information useful to achieve a better QoL.

Discussing and treating sexual problems in stroke survivors enters the framework of a holistic approach. Prevention should dispel stereotypes, myths, and misperceptions, not only in stroke survivors and their partners but also in rehabilitation staff members who may be unprepared for this goal.

References

[1] Gray LJ, Sprigg N, Bath PM, Boysen G, De Deyn PP, Leys D, O'Neill D, Ringelstein EB; TAIST Investigators. Sex differences in quality of life in stroke survivors: data from the Tinzaparin in Acute Ischaemic Stroke Trial (TAIST). *Stroke*. 2007;38:2960-4.

[2] Darlington AS, Dippel DW, Ribbers GM, van Balen R, Passchier J, Busschbach JJ. Coping strategies as determinants of quality of life in stroke patients: a longitudinal study. *Cerebrovasc Dis*. 2007;23:401-7.

[3] Moon YS, Kim SJ, Kim HC, Won MH, Kim DH. Correlates of quality of life after stroke. *J. Neurol. Sci.* 2004; 224:37-41.

[4] Pistoia F, Govoni S, Boselli C. Sex after stroke: a CNS only dysfunction? *Pharmacol. Res*. 2006; 54:11-8. Review

[5] Rees PM, Fowler CJ, Maas CP. Sexual function in men and women with neurological disorders. *Lancet*. 2007;369:512-25. Review

[6] Monga TN, Lawson JS, Inglis J. Sexual dysfunction in stroke patients. *Arch. Phys. Med. Rehabil*. 1986; 67:19-22.

[7] Boldrini P, Basaglia N, Calanca MC Sexual changes in hemiparetic patients. *Arch. Phys. Med. Rehabil*. 1991;72:202-7

[8] Tamam Y, Tamam L, Akil E, Yasan A, Tamam B. Post-stroke sexual functioning in first stroke patients. *Eur. J. Neurol*. 2008;15:660-6.

[9] Giaquinto S, Buzzelli S, Di Francesco L, Nolfe G Evaluation of sexual changes after stroke. *J. Clin. Psychiatry*. 2003;64:302-7

[10] Korpelainen JT, Nieminen P, Myllylä VV. Sexual functioning among stroke patients and their spouses. *Stroke*. 1999;30:715-9.

[11] Korpelainen JT, Kauhanen ML, Kemola H, Malinen U, Myllylä VV. Sexual dysfunction in stroke patients. *Acta Neurol. Scand*. 1998;98:400-5.

[12] Sjögren K, Fugl-Meyer AR.Sexual problems in hemiplegia.*Int. Rehabil. Med*.1981;3:26-31

[13] Cheung RT. Sexual functioning in Chinese stroke patients with mild or no disability. *Cerebrovasc. Dis.* 2002;14:122-8.

[14] Agarwal A, Jain DC. Male sexual dysfunction after stroke. *J Assoc Physicians. India*.1989; 37:505-7.

[15] Coslett HB, Heilman KM. Male sexual function. Impairment after right hemisphere stroke. *Arch. Neurol*. 1986;43:1036-9.

[16] Daniele A, Azzoni A, Bizzi A, Rossi A, Gainotti G, Mazza S. Sexual behavior and hemispheric laterality of the focus in patients with temporal lobe epilepsy. *Biol. Psychiatry* 1997;42:617-24

[17] Jung JH, Kam SC, Choi SM, Jae SU, Lee SH, Hyun JS. Sexual dysfunction in male stroke patients: correlation between brain lesions and sexual function. *Urology*. 2008;71:99-103

[18] Jeon SW, Yoo KH, Kim TH, Kim JI, Lee CH.Correlation of the erectile dysfunction with lesions of cerebrovascular accidents. *J. Sex. Med*. 2009; 6:251-6

[19] Goddess ED, Wagner NN, Silverman D. Post stroke activity in CVA patients. *Med. Aspects Human. Sex.* 1979;13:16-30.

[20] Monga TN, Monga M, Raina MS, Hardjasudarma M. Hypersexuality in stroke. *Arch. Phys. Med. Rehabil*. 1986;67:415-7.

[21] Mutarelli EG, Omuro AM, Adoni T.Hypersexuality following bilateral thalamic infarction: case report. *Arq. Neuropsiquiatr*. 2006;64:146-8.

[22] Absher JR, Vogt BA, Clark DG, Flowers DL, Gorman DG, Keyes JW, Wood FB. Hypersexuality and hemiballism due to subthalamic infarction. *Neuropsychiatry Neuropsychol. Behav. Neurol.* 2000;13:220-9.

[23] Jawad S, Sidebothams C, Sequira R, Jamil N. Altered sexual orientation following dominant hemisphere infarct. *J. Neuropsychiatry Clin. Neurosci*. 2009;21:353-4.

[24] Ong Hai BG, Odderson IR. Involuntary masturbation as a manifestation of stroke-related alien hand syndrome. *Am. J. Phys. Med. Rehabil*. 2000;7:395-8

[25] Choi-Kwon S, Kim JS. Poststroke emotional incontinence and decreased sexual activity. *Cerebrovasc. Dis*. 2002;13(1):31-7

[26] Kautz DD. Hope for love: practical advice for intimacy and sex after stroke. *Rehabil. Nurs.* 2007; 32:95-103; discussion 132. Review

[27] Bener A, Al-Hamaq AO, Kamran S, Al-Ansari A. Prevalence of erectile dysfunction in male stroke patients, and associated co-morbidities and risk factors. *Int. Urol. Nephrol*. 2008;40:701-8

[28] Kimura M, Murata Y, Shimoda K, Robinson RG. Sexual dysfunction following stroke. *Compr. Psychiatry*. 2001;42:217-22

[29] Bancroft J, Janssen E. The dual control model of male sexual response: a theoretical approach to centrally mediated erectile dysfunction. *Neurosci. Biobehav. Rev*. 2000;24:571-9.

[30] Duits A, van Oirschot N, van Oostenbrugge RJ, van Lankveld J. The relevance of sexual responsiveness to sexual function in male stroke patients. *J .Sex Med*. 2009;6:3320-6

[31] Wade DT, Legh-Smith J, Hewer RL Effects of living with and looking after survivors of a stroke. *Br. Med. J. (Clin Res Ed).* 1986;293:418-20

[32] Kinsella GJ, Duffy FD Psychosocial readjustment in the spouses of aphasic patients. A comparative Survey of 79 subjects. *Scand J. Rehabil. Med*. 1979;11:129-32

[33] Sjögren K.Sexuality after stroke with hemiplegia. II. With special regard to partnership adjustment and to fulfilment. *Scand. J. Rehabil. Med*. 1983;15:63-9

[34] Korpelainen JT, Sotaniemi KA, Myllylä VV. Autonomic nervous system disorders in stroke. *Clin. Auton. Res.* 1999;9:325-33.

[35] Lemieux L, Cohen- Schneider R, Holzapfel S. Aphasia and Sexuality. *Sexuality and Disability.* 2001; 19: 253-266.

[36] Koton S, Tanne D, Bornstein NM, Green MS.Triggering risk factors for ischemic stroke: a case-crossover study. *Neurology*. 2004;63:2006-10.

[37] Adams HP Jr. Patent foramen ovale: paradoxical embolism and paradoxical data. *Mayo Clin. Proc*. 2004;79:15-20.

[38] Ebrahim S, May M, Ben Shlomo Y, McCarron P, Frankel S, Yarnell J, Davey Smith G. Sexual intercourse and risk of ischaemic stroke and coronary heart disease: the Caerphilly study. *J. Epidemiol. Community Health.* 2002;56:99-102.

In: Male Sexual Dysfunctions in Neurological Diseases… ISBN 978-1-61761-855-0
Editor: Calabrò Rocco Salvatore

Chapter 6

Sexual Dysfunction in Multiple Sclerosis

Lorenzo De Santi, Edoardo Sessa and Rocco Salvatore Calabrò

Abstract

Sexuality and sexual health are important factors in determining quality of life. Multiple sclerosis (MS), a major cause of neurological disability in young adults, can compromise the perception, definition and expression of sexuality. Physical and cognitive symptoms of MS as well as psychological and social issues can directly affect sexual functioning and body image with reduced libido and self-esteem. Male patients with MS frequently develop sexual dysfunction (SD) as a consequence of the neurological impairment, physical and psychological changes indirectly affecting the sexual response. Recently, a greater attention for SD in physicians involved in the care of MS has led to the improvement of diagnostic and therapeutic options for SD. In parallel with the optimization of disease-modifying and symptomatic therapies for MS improving long-term functional independence, advances in medical and surgical treatments for neurogenic SD could enhance quality of life.

The first part of this chapter discusses the epidemiology and pathophysiology of SD in male patients. The second part addresses the diagnostic and therapeutic approaches, with regard to both standardized clinical diagnostic instruments and upcoming imaging techniques, and multidisciplinary treatment strategies.

Introduction

Multiple sclerosis (MS) is a common inflammatory disorder of the central nervous system affecting about 2.5 million people around the world. MS represents the most common cause of neurological disability among young adults [1]. In the relapsing-remitting (RR) phase, MS is generally characterized by acute attacks spontaneously resolving or leaving chronic neurological consequences. In the secondary progressive (SP) phase, patients undergo

a slow progression of disability with or without superimposed relapses. In this *scenario,* patients with MS suffer from neurological sequelae of relapses and chronic progression, and residual symptoms related to new lesion formation. Although patent therapies for MS - i.e. interferons beta, glatiramer acetate and, more recently, natalizumab - have dramatically changed the natural history of MS by reducing the number of relapses and the progression of clinical disability [2], the management of specific symptoms encountered by MS patients, including spasticity or muscle weakness, pain, tremor, fatigue, sensory deficits, bladder dysfunction and cognitive impairment, is still challenging. Sexual dysfunction (SD), especially in male patients, is another frequent and disabling aspect of the disease, severely affecting quality of life, mood and interpersonal relationships. The negative impact of SD on quality of life in MS has been recently demonstrated even when corrected by confounding factors such as disability, as evaluated by the Expanded Disability Status Scale (EDSS) [3] and age [4,5]. Unfortunately, SD is frequently overlooked and, as a consequence, not faced and managed properly. In MS, the reason for the underestimation of this problem can be attributed both to patients, often reticent to address these symptoms to the medical staff, and neurologists, that do not approach the topic systematically.

In recent years, a comprehensive conceptual model of SD in MS has been developed by Foley et al. [6]. This model categorizes SD in three general components: primary, secondary and tertiary SD. The primary SD is directly due to MS-related neurologic deficits affecting the sexual response. Men complain of altered genital sensation, decreased libido, ejaculation and orgasmic dysfunction and, most commonly, erectile dysfunction (ED). The secondary SD is attributed to MS-related physical impairments and symptoms that affect indirectly the sexual response, including spasticity and contractures, fatigue, bladder dysfunction and cognitive symptoms. Furthermore, adverse effects of MS medications are frequently causes of secondary SD. The tertiary SD is caused by the psychological, social and cultural issues of having a chronic disabling disease that affects sexual functioning. Symptoms of MS may compromise the self-image affecting the way one views himself as an attractive individual. An impaired self-esteem can generate fear of rejection, decreased sexual confidence causing withdrawal from sexual activity. In addition, mood disorders and emotional issues such as anxiety and guilt can have a negative effect on sexuality and intimate relationship. The examination of SD according to this model allows a better identification of the nature of symptoms and the specific cause of the problem, focusing on the appropriate treatment approach.

In the first part of this chapter we will discuss the prevalence and the pathophysiology of SD in male patients with MS. In the second part we will review the basic intervention in the evaluation and treatment of SD.

The aim of this chapter is to show the principles underlying a correct, comprehensive and multifactorial approach to alleviate symptoms of SD and improve the quality of life in male MS patients.

Prevalence of Male Sexual Dysfunction in Multiple Sclerosis

Historically, clinical studies have reported a prevalence of SD in male patients with MS ranging from 7% to 91% [7,8]. More recent studies have confirmed a high prevalence of SD in men, ranging from 45% to 70% [9,10]. SD prevalence is significantly higher in MS

patients than in the general population [11]. In a large case-control study [9], male patients with MS experienced decreased libido, erectile dysfunction (ED) and ejaculatory dysfunction with a higher frequency than patients with other chronic diseases or healthy controls.

As previously described, primary SD accounts for MS-related neurologic alterations, directly compromising sexuality. ED was empirically considered for years the most frequent SD reported by men with MS. MS male patients complain of ED in 50%-75% of cases. Another frequent SD is ejaculatory dysfunction often associated to orgasmic dysfunction (including premature, retarded or retrograde ejaculation) (50%) and anorgasmia (37%) [6,12]. Men often reported decreased sexual interest or desire (libido) as a common event (39%) during the course of MS.[6]

Regarding secondary and tertiary SD, prevalence estimates are relatively more difficult than for primary SD. Secondary SD is a consequence of MS symptoms or an adverse effect of symptomatic drugs, and does not directly affect pathways related to the neurologic control of the genital system. Some Authors reported from their anecdotal experience that the prevalence of secondary SD may be correlated with the prevalence of specific symptoms [13]. Secondary symptoms of MS most frequently impairing sexual activity are muscle weakness (58%), spasticity (24%), contractures (12%), incontinence (5%) [14]. MS patients with spasticity can experience adductor spasms during intercourse, leading to difficulty with movements, fatigue and pain affecting about 75% and 70% of patients, respectively, that may discourage them from engaging in sexual activity. Neurogenic bladder symptoms – i.e. urinary frequency, urgency, incontinence, retention – are frequently associated with SD and about 98% of MS male patients with ED reported urinary symptoms in the study of [15]. Cognitive dysfunction has been recognized as an early symptom in MS patients (45%-65%) [16]. As sexuality, with regard to its psychological aspects, depends widely on higher cortical function, some Authors highlighted a frequent correlation between cognitive dysfunction and SD [13]. In addition to MS-related symptoms, many symptomatic treatments currently used in the clinical practice – antispastics, anticonvulsivants, antidepressants - may have the potential to cause urinary disturbances, ED, decreased libido and precipitating secondary SD.

Regarding tertiary SD, mood disorders, mainly depression, that affects 24% to 54% of patients, contribute to SD.

Prevalence of SD has also been studied in different subtypes of MS and in patients with different levels of disability. No studies have shown a clear association between ED and MS subtypes [17,18]. Numerous studies have demonstrated a positive correlation between SD and disease duration and disability [10,5,19,20], while others failed to find positive correlations between high EDSS score and SD [11,21,22]. The correlation between disability and SD is still uncertain. In line with these controversial findings, the study of MacCabe et al. [11] did not demonstrate a correlation between MS exacerbations and sexual satisfaction.

Pathophysiology of Male Sexual Dysfunction in Multiple Sclerosis

Erection and ejaculation are the result of the interaction of sensitive stimuli involving the penis. The spinal and peripheral innervation of the penis includes somatic afferences and sympathetic and parasympathetic nervous systems. Afferences from the penis mainly synapse

at S2-S4 level but some fibers ascend and enter the spinal cord in the lower thoracic region with sympathetic ones. Parasympathetic efference causes vasodilatation in erectile tissue. Ejaculation starts as the result of pudendal somatic motor and sympathetic innervation causing contractions of the pelvic floor and propulsion of the semen while the bladder neck is closed.

Normally, sexual activity depends upon the interaction between neurological, endocrine, vascular and psychological factors. Sexual function includes arousal, peripheral response of the genitals (vascular congestion and erection) and orgasm. In MS, both lesions involving the brain and spinal cord can be the cause of SD. The higher frequency of primary SD in MS patients rather than in the general population accounts for a major role of neurological damage caused by MS in the pathogenesis of these disturbances [9]. Arousal has been demonstrated to start centrally and Magnetic Resonance Imaging (MRI) studies have begun to identify a number of brain regions that take part in this process. Upper motor neuron lesions in the brainstem or above the lumbar section of the spinal cord may compromise psychogenic erection [22]. Furthermore, MS brain lesion can directly interfere with the regulation of libido and the arousing of sexual stimuli [23]. Various MRI studies have tried to correlate the burden and location of MS-related plaques to SD, with the aim to also separate organic from psychogenic etiologies of SD in MS patients. Even if MRI studies still need further validation, demyelinating lesions of the pons are emerging as predictive markers of SD, especially orgasmic dysfunction. Zivadinov et al. [20] found a significant correlation between parenchymal atrophy of the pons and ED in male patients with MS. In the same study, no other MRI measures, including T1 and T2 lesion burden and cortical atrophy, and neurophysiologic studies (cortical pudendal and tibia evoked potentials) correlated with symptoms of SD. Other Authors confirmed the correlations between SD and pontine atrophy and demonstrated correlations between SD and the cerebral white matter lesion burden of the inferior parietal lobe and ventricle enlargement [21]. Brainstem and pyramidal alterations, as well as MRI total lesion burden, have been particularly correlated with anorgasmia in patients with MS [12]. The use of a multimodal ascertainment (evoked potentials, MRI) in the evaluation of SD in MS could enhance our ability to predict the onset and the evolution of primary SD. The potential for particular MRI parameters in the study of SD in MS, especially primary SD, is increasing and, even if still not validated, could represent the future of SD diagnostics and follow-up.

As the same neurological pathways compromised in bladder and bowel functions are also involved in sexual function, a possible correlation between these disturbances and SD has been widely investigated [5,12]. Bladder and bowel dysfunctions, including constipation, evacuation, diarrhea and fecal incontinence are common in MS, with a frequency of 83% and 45%-68%, respectively [22]. Some studies reported a correlation between bladder symptoms and ED. However, this was not confirmed by studies correlating data of urodynamic tests with ED in male MS patients [24]. Generally, a strong correlation between the presence and severity of neurologic bladder with SD has been established, independently from the disability score (EDSS) and age [22]. In addition, other studies revealed interesting associations between specific bladder dysfunctions (urgency, urge incontinence…) and those of SD (altered genital sensation, decreased libido and orgasm, increased time for arousal, ED). However, despite the high prevalence of bladder and bowel disturbances in MS, studies have provided no clear evidence of an etiological relationship between these disturbances and SD.

Evaluation of Sexual Dysfunction in Multiple Sclerosis

The evaluation of SD in male patients with MS should start with a comprehensive history collection and physical examination. The ideal approach to MS patients experiencing SD is multidisciplinary, involving different professional workers as nurses, social workers and psychologists coordinated by the neurologist, highly trained in SD and MS. The high prevalence of SD in MS patients and the lack of symptoms or diagnostic tools predictive of primary SD onset point out the need of an accurate sexual history collection.

Clinical Interview

A semi-structured clinical interview is the first and mandatory tool to investigate the presence of SD in MS patients. The objectives of the clinical interview are the identification of the SD and the evaluation of its severity and impact on quality of life. A comprehensive evaluation necessarily deals with the nature of the main sexual complaint, the time of onset, its frequency and severity, information about religious, cultural, social and sexual orientation of the patient, lifestyle issues (eating habits, alcohol and/or drug abuse, exercise and work habits), medical information regarding MS (recent relapses, medical disorders potentially causing SD, bladder or bowel dysfunction) and psychological information (problems experienced during past relationships, emotional status, presence of anxiety or mood disorders, history of mental illness, decreased self-esteem and/or altered body image, presence of psychological stressors). It is also of great importance to investigate the past medical history regarding any previous SD treatment and the attempted strategies of management, including consults with neurologists, psychosexuologists and/or psychiatrists and the goals that were or were not reached by the treatment. Each individual may have different expectations for treatments and this should accurately be discussed and planned during the consult with the managing team.

These semi-structured clinical interview may provide a general scheme to obtain essential data on the patient‘s sexual life. However, this interview should be personalized, supplemented and modified by the clinician according to personal experience and the patient’s situation.

Standardized Questionnaires

Despite the current use of semi-structured clinical interviews for the assessment of SD, a practical and validated instrument for the quantification of SD is still lacking in the literature. As a consequence, in recent years researchers and clinicians have used questionnaires and surveys that are not standardized or validated, including The Sexual Function Scale of the Minimal Record of Disability (MRD) [24]. This part of the MRD scale is useful in the assessment of the general level of sexual activity distinguishing between before and after the onset of MS. However, this questionnaire falls short in categorizing the specific nature of sexual symptoms, severity and their impact on sexual functioning. In 2000, a 9-item self-

reported structured questionnaire, The Multiple Sclerosis Intimacy and Sexuality Questionnaire (MSISQ), was developed [13]. It is based on the conceptual model of Foley et al. and it is conceived to assess the impact of primary, secondary and tertiary symptoms on sexual activity and satisfaction. This scale is easy to use and very reliable and allows the clinician to underlie specific areas of SD and the severity of their involvement.

It is a suitable screening tool for SD, preliminary to a more comprehensive treatment planning both in men and women. Regarding ED, a structured reliable symptom collection can be obtained through The International Index of Erectile Function (IIEF), a self-administered questionnaire.

Medical Assessment

Medical examination for the assessment of SD should be comprehensive and include all systems potentially involved in the physiology of sexuality. Neurologic examination should include the assessment of genital sensitive function including the research for allodynia, muscle weakness and alterations in muscular tone and the anal wink to document reflex function of the sacral segments.

Physical examination should also be accurately performed as it may reveal potential signs of medical conditions associated to SD. A decline in body hair, gynecomastia and testicular atrophy can signal a decreased sieric androgen level. Scars as signs of prior abdominal surgery, the presence of bruits at the auscultation of femoral pulses may indicate a possible cause of neurovascular dysfunction. Orthostatic hypotension may discover an autonomic nervous system dysfunction. External examination of the penis is also important as it can reveal anatomic abnormalities that can be secondary to diseases (i.e. Peyronie's disease), trauma or surgery.

MRI of the brain and entire spinal cord should be performed. Electrophysiological examination is based on the bulbocavernosus reflex that may reveal a disruption in either the central sacral reflex center or the pudendal/penile nerves. It should be accompanied by the evoked somatosensory reflex of the pudendal plexus. In the case of ED, nocturnal penile tumescence (NPT) should also be assessed as a simple and non-invasive method to distinguish psychogenic component of ED. This test can document the preserved nocturnal reflex erection in psychogenic ED. However, it may sometimes give false positive results in patients with purely neurogenic ED. Psychogenic ED generally develops acutely, could be intermittent or present only with selected partners, with the preservation of the ability to masturbate and to achieve morning erections. Most MS patients with ED continue to have nocturnal erections or erections in response to genital stimulation without being sufficient for sexual intercourse. Organic causes of ED other than MS include medical conditions such as diabetes mellitus, atherosclerosis, hyper or hypothyroidism, hypertension, uremia, alcoholism, vasculopathy, neuropathy and hypogonadism. In MS, male patients experiencing ED are generally young and have no other risk factors for ED. On the other hand, all these conditions should be excluded or confirmed, as neurogenic ED is not predicted by any test, and it is diagnosed by exclusion. However, organic and psychogenic ED can coexist and the identification of an organic cause cannot exclude the presence of psychological stressors.

A complete review of medication regimen is crucial to exclude iatrogenic causes of SD. A great variety of symptomatic drugs commonly used in MS are recognized causes of SD (Table 1).

Table 1. Adverse sexual effects of frequently used symptomatic drugs for multiple sclerosis

Symptoms of MS	Treatment	Adverse sexual function effects
Spasticity	Baclofen	ED Inability to ejaculate
	Tizanidine	Urinary frequency Urgency Incontinence Urinary retention
	Dantrolene	Decreased libido ED Retrograde ejaculation
Fatigue	Amantadine	Decreased libido
Pain	Tricyclic antidepressants	ED Ejaculatory impairment Anorgasmia Decreased libido
	Valproic acid Carbamazepine Gabapentin Levetiracetam Lamotrigine	ED ED ED ED ED
	Duloxetine	Decreased libido ED Ejaculation dysfunction Anorgasmia
Depression	SSRIs	Decreased libido Anorgasmia Delayed ejaculation
	Venlafaxine	ED Anorgasmia

ED: erectile dysfunction; MS: multiple sclerosis; SSRIs: selective serotonin reuptake inhibitors.

Antispastics can induce several SDs including ED and inability to ejaculate (Baclofen), urinary frequency, urgency, retention and incontinence (Tizanidine), ED, retrograde ejaculation end decreased libido (Dantrolene). Amantadine, the most frequently used drug treatment for fatigue may determine decreased libido. Also anticonvulsants such as carbamazepine or phenytoin may lower serum levels of testosterone and, subsequently, libido. Other anticonvulsant or antidepressant drugs commonly used for the treatment of seizures, depression or neuropathic pain are associated to a large number of adverse sexual side effects including ED, ejaculatory impairment and anorgasmia, decreased libido (tricyclic antidepressants, selective serotonine reuptake inhibitors, venlafaxine), ED (valproic acid, lamotrigine, duloxetine, gabapentin, levetiracetam). A possible treatment strategy could be represented by the tapering of dose and the substitution with alternative agents. A comprehensive review addressing the potential adverse side effects of symptomatic drugs for MS has been recently published by Fletcher et al. (2008) [13].

Multidisciplinary Approach to Sexual Dysfunction in Multiple Sclerosis

At this time, no approved disease-modifying drugs for MS are effective in improving or preventing SD. As a consequence, neurologists must be confident of all treatment options globally regarding aspects of sexuality, their short- and long-term consequences and should be realistic with the patient about expectancies. The "right" choice of the most satisfying treatment for SD necessarily implies the collaborative efforts of the neurologist, the patient and his partner. In addition, nurses and social workers should be involved in the decision making process to tailor-make treatment plans that are not only effective but also coincide with the patient's lifestyle, cultural and religious values.

Primary Sexual Dysfunction

ED is the most frequently reported SD in male patients with MS. ED can be approached and often successfully treated by a variety of methods. Pharmacological approaches are affective and represent a well-tolerated treatment for neurogenic ED of various etiologies. Sildenafil citrate is a phosphodiesterase type 5 inhibitor, acting on the cavernosal smooth muscle of the penis and enhancing erectile function subsequently to sexual stimulation that showed a significant improvement of erections in a double blind randomized trial compared with placebo [25]. Penile erection is mediated by nitric oxide via cyclic guanosine monophosphate (cGMP). Sildenafil improves cGMP concentrations locally in the penis, promoting tumescence. More recently, other phosphodiesterase type 5 inhibitors, such as vardenafil and tadalafil, have been introduced in clinical practice. These compounds have a longer half-life than sildenafil, allowing more spontaneous erections and a long-lasting efficacy. Another pharmacological treatment for neurogenic impotence is intracavernosal injection of vasodilatatory agents. The most commonly used agents are alprostadil (prostaglandin E1) and papaverine. Injections are performed through a small-gauge needle at the base of the penis into each corporal body. Slow infusion is associated to a minimum discomfort and automated self-injection devices simplify the process. Most MS patients experiencing ED are young, with an adequate blood flow to the corpora cavernosa, showing a good response to intracavernosal injections at low doses. Prostaglandin E1 is endogenously produced in the penis and determines a more natural erection with a lower complication rate. Possible side effects associated to this treatment are local scar formation, impaired integrity of neurovascular tissue and deformity of the penis, priapism. Prostaglandin E1 may also be administered by urethral suppositories and this route of administration can be chosen by patients with motor limitations and poor hand coordination. Combination of alprostadil, papaverine and phentolamine has not been studied yet in men with MS experiencing ED; however, given the good results obtained in young patients with other causes of neurogenic ED, 95% of success rate in patients with spinal cord injury [26], it should be effective also in MS patients.

Vacuum devices or "pumps" are non surgical alternatives to the pharmacological treatment of neurogenic ED. These devices are placed over the flaccid penis to create a vacuum that induces blood flow into the penis causing the erection. When the erection is

achieved a band is placed at the basis of the penis to prevent the flowing back of the blood. These devices have been studied in patients with spinal cord injury and the percentage of men showing an erection adequate for penetration was 93% and 76% at three and six months, respectively [27]. The most common adverse effects associated to the use of vacuum devices are premature loss of erection, ecchymosis, petechiae, skin abrasions, discomfort. These devices have not been studied in the MS population and data about efficacy and safety are derived from studies on cohorts of patients with spinal cord injury.

Surgical alternatives for neurogenic ED are several types of inflatable and non-inflatable penile implants. Non-inflatable implants consist of semirigid flexible rods surgically placed into the corpora cavernosa allowing the penis to simulate a natural erection. The limitation of this surgery is that the penis is in a permanent semirigid state and smaller than a naturally erected penis. In inflatable prostheses, a fluid-filled reservoir is implanted in the lower abdomen and connected to tubes in the corpora cavernosa of the penis. With the pressure applied to the pump, the fluid flows from the reservoir to the tubes in the penis to simulate a natural erection. When erection is not needed a valve on the pump lets the fluid flow back and the penis return flaccid. These devices are more expensive than the non-inflatable prostheses and this surgery is more invasive.

In some MS patients with neurogenic ED, the inability to achieve a reliable erection could be due to a somatosensory deficit and reversed by a vibratory stimulation to the glans penis or applied through a rectal probe. If the erection obtained with the electrostimulator is inadequate for vaginal penetration, other agents, including the previously reviewed pharmacological phosphodiesterase type 5 inhibitors, can be used in association.

Other new treatments for neurogenic ED are under investigation. Transanal electrical stimulation to the pelvic plexus has shown the ability to induce a semi-rigid or rigid erection in 57% of patients with non-neurogenic ED [28] and percutaneous perineal electrostimulation resulted in a significant increase in intracavernosal pressure in 18 young men with spinal cord injury and ED and healthy controls [29]. These new techniques could provide new and non-invasive alternative strategies for the management of neurogenic ED.

Secondary Sexual Dysfunction

As previously discussed, secondary SD is a direct consequence of symptoms and physical limitations due to MS. A correct information and education is crucial to help patients to manage their secondary SD. Simple suggestions like the planning of daily activities can significantly reduce the impact of symptoms on sexuality.

To alleviate fatigue, oral drugs with a stimulatory effect, such as amantadine or pemoline, can be taken before sexual activity. Other strategies deal with the planning of energy-saving techniques during daily activities or choosing sexual positions that are less difficult and strenuous for the partners with MS. Muscle weakness, spasticity, and incoordination may be greatly influenced by sexual position. The aid of counseling by a physical therapist experienced in sexual issues may be helpful for the couple to find safe and comfortable positions to engage in sexual activity. In addition, the use of antispastic medications before sexual activity can reduce difficulties due to spasticity. A correct choice of position for sexual activity is also of great importance when bladder dysfunction is present. In this case

occupational therapists and nurses should teach MS patients how to avoid positions that put pressure on the bladder and bladder devices and how to manage catheters before and during the sexual intercourse. Bladder dysfunction can severely compromise the quality and the continuity of sexual activity. Patients should avoid drinking and empty the bladder before having sex. To make the sexual activity more relaxing and to reduce anxiety, psychotherapists should discuss with the patient and his partner about possible accidents associated with the loss of bladder or bowel control during sex. This would reduce embarrassment and fear of rejection by the partner.

Medications frequently used in MS as symptomatic drugs can interfere with a variety of aspects of sexual activity as described in the paragraph "Evaluation of sexual dysfunction in multiple sclerosis: medical assessment". In every single case, the neurologist should assess the benefits of medications on the overall quality of life, taking into account their possible influence on sexual activity. If the pharmacological treatment impairs sexual performance, the neurologist should choose an alternative drug or try to modify dosages or administration schedule to reduce the negative effect on sexuality.

Tertiary Sexual Dysfunction

MS is a chronic disabling disease that affects sexual functioning. This condition has psychological, social and cultural implications that generate tertiary SD. Symptoms of MS may compromise the self-image affecting the way one views himself as an attractive individual associated to feeling less masculine, diminished sexual confidence and reactive depression, anxiety and decreased libido. A therapeutic intervention involving psychotherapists, psychologists and social workers may improve self-esteem by providing positive feedback, reinforcement and adequate copying strategies. The need for dependency can make the patient feel vulnerable and angered. On the other hand, partners may be resentful of their acquired responsibilities and their new role of care-giver. Effective communication into couples facing MS is essential for expressing personal fears and needs related to sexual activity and maintaining a healthy partnership. Communication skills are improved by couple counseling, favoring better copying strategies of patients with chronic diseases such as MS. In addition, the nursing activity should be performed, if at all possible, by non family members, as it allows the partner to preserve his identity as sexual partners.

Conclusions

SD shows a high prevalence among the male population with MS. SD is caused by the involvement of specific neuropsychological processes regarding sexual function and by the influences of symptoms and physical disability due to MS. The exact mechanisms are still under investigation. The categorization of SD by Foley et al. into three classes – primary, secondary and tertiary SDs – has improved our ability to understand, approach and manage their complex and multifactorial nature. An accurate diagnosis of the causes and nature of the SD is necessary for an effective treatment strategy that should include a combination of medical (pharmacological and/or surgical), educational and counseling approaches, as well as

practical hints for daily living and sexual activities. Categorizing the SDs as primary, i.e. directly regarding neurological damage due to MS, or secondary, i.e. as a consequence of symptoms or drug side effects, or tertiary, i.e. the psychological and social implications of MS affecting sexual functioning, is possible only with an open and direct patient-doctor communication. Neurologists and coworkers (nurses, psychologists, social workers) trained in MS should take the initiative in asking patients about their sexual functioning and possible dysfunctions, quantifying the degree of impairment and its impact on quality of life and finding the best approach. To date, the best approach to alleviate clinical symptoms is based on an open communication between the patient and the team managing MS, followed by a multidisciplinary approach.

References

[1] Compston, A; Coles, A. Multiple sclerosis. *Lancet*, 2008, 372(9648),1502-17.

[2] Trojano, M; Pellegrini, F; Fuiani, A et al. New natural history of interferon-beta-treated relapsing multiple sclerosis. *Ann. Neurol.*, 2007, 61(4), 300-6.

[3] Kurtzke, JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). *Neurology*, 1983, 33(11), 1444-52.

[4] Miller, A; Dishon, S. Health-related quality of life in multiple sclerosis: The impact of disability, gender and employment status. *Qual. Life Res.*, 2006, 15(2), 259-271.

[5] Nortvedt, MW; Riise, T; Myhr, KM, et al. Reduced quality of life among multiple sclerosis patients with sexual disturbance and bladder dysfunction. *Mult. Scler*, 2001, 7(4), 231-5.

[6] Mattson, D; Petrie, M; Srivastava, DK; McDermott, M. Multiple sclerosis. Sexual dysfunction and its response to medications. *Arch. Neurol.*, 1995, 52(9), 862-8.

[7] Lilius, HG; Valtonen, EJ; Wikström, J. Sexual problems in patients suffering from multiple sclerosis. *Scand J. Soc. Med.*, 1976, 4(1), 41-4.

[8] Lilius, HG; Valtonen, EJ; Wikström, J. Sexual problems in patients suffering from multiple sclerosis. *J .Chronic. Dis*, 1976, 29(10), 643-7.

[9] Zorzon, M; Zivadinov, R; Monti Bragadin, L, et al. Sexual dysfunction in multiple sclerosis: a 2-year follow-up study. *J. Neurol. Sci*, 2001, 187(1-2), 1-5.

[10] Demirkiran, M; Sarica, Y; Uguz, S; Yerdelen, D; Aslan, K. Multiple sclerosis patients with and without sexual dysfunction: are there any differences? *Mult. Scler*. 2006, 12(2), 209-14.

[11] McCabe, MP. Exacerbation of symptoms among people with multiple sclerosis: impact on sexuality and relationships over time. *Arch. Sex Behav.*, 2004, 33(6), 593-601.

[12] Barak, Y; Achiron, A; Elizur, A, et al. Sexual dysfunction in relapsing-remitting multiple sclerosis: magnetic resonance imaging, clinical, and psychological correlates. *J. Psychiatry Neurosci*,. 1996, 21(4), 255-8.

[13] Fletcher, SG; Castro-Borrero, W; Remington, G, et al. Sexual dysfunction in patients with multiple sclerosis: a multidisciplinary approach to evaluation and management. *Nat. Clin. Pract. Urol*,. 2009, 6(2), 96-107.

[14] Valleroy, ML; Kraft, GH. Sexual dysfunction in multiple sclerosis. *Arch .Phys .Med. Rehabil.*, 1984, 65(3), 125-8.

[15] Betts, CD. Pathophysiology of male sexual dysfunction in multiple sclerosis. *Sex Dis.*, 1996, 14(1), 41-55.

[16] Rao, SM; Leo, GJ; Bernardin, L; Unverzagt, F. Cognitive dysfunction in multiple sclerosis. I. Frequency, patterns, and prediction. *Neurology*, 1991, 41(5), 685-91.

[17] Yang, CC; Bowen, JR; Kraft, GH; Uchio, EM; Kromm, BG. Cortical evoked potentials of the dorsal nerve of the clitoris and female sexual dysfunction in multiple sclerosis. *J. Urol.*, 2000;164(6):2010-2013.

[18] McDougall, AJ; McLeod, JG. Autonomic nervous system function in multiple sclerosis. *J. Neurol. Sci.*, 2003, 215(1-2), 79-85.

[19] Hulter, BM; Lundberg, PO. Sexual function in women with advanced multiple sclerosis. *J. Neurol. Neurosurg. Psychiatr.*, 1995, 59(1), 83-6.

[20] Zivadinov, R; Zorzon, M; Locatelli, L, et al. Sexual dysfunction in multiple sclerosis: a MRI, neurophysiological and urodynamic study. *J. Neurol. Sci.*, 2003, 210(1-2), 73-6.

[21] Janardhan, V; Bakshi, R. Quality of life and its relationship to brain lesions and atrophy on magnetic resonance images in 60 patients with multiple sclerosis. *Arch. Neurol*, 2000, 57(10), 1485-91.

[22] Dewis, ME; Thornton, NG. Sexual dysfunction in multiple sclerosis. *J. Neurosci. Nurs.*, 1989, 21(3), 175-9.

[23] DeLisa, JA; Miller, RM; Mikulic, MA; Hammond, MC. Multiple sclerosis: Part II. Common functional problems and rehabilitation. *Am. Fam. Physician*. 1985, 32(5), 127-32.

[24] Lottman, PE; Jongen, PJ; Rosier, PF; Meuleman, EJ. Sexual dysfunction in men with multiple sclerosis--a comprehensive pilot-study into etiology. *Int. J. Impot. Res.*, 1998, 10(4), 233-7.

[25] Fowler, CJ; Miller, JR; Sharief, MK, et al. A double blind, randomised study of sildenafil citrate for erectile dysfunction in men with multiple sclerosis. *J. Neurol. Neurosurg. Psychiatr.*, 2005, 76(5), 700-5.

[26] Bodner, DR; Haas, CA; Krueger, B; Seftel, AD. Intraurethral alprostadil for treatment of erectile dysfunction in patients with spinal cord injury. *Urology*, 1999, 53(1), 199-202.

[27] Denil, J; Ohl, DA; Smythe, C. Vacuum erection device in spinal cord injured men: patient and partner satisfaction. *Arch. Phys. Med. Rehabil.*, 1996, 77(8), 750-3.

[28] Kayigil, O; Agras, K; Gurdal, M, et al. Effects of transanal pelvic plexus stimulation on penile erection: clinical implications. *Int. Urol. Nephrol.*, 2007, 39(4), 1195-201.

[29] Shafik, A; Shafik, AA; Shafik, IA; El Sibai, O. Percutaneous perineal electrostimulation induces erection: clinical significance in patients with spinal cord injury and erectile dysfunction. *J. Spinal Cord Med.*, 2008, 31(1), 40-3.

In: Male Sexual Dysfunctions in Neurological Diseases… ISBN 978-1-61761-855-0
Editor: Calabrò Rocco Salvatore

Chapter 7

Sexuality in Neurodegenerative Disorders

Silvia Marino, Francesco Cordici, Annalisa Baglieri, Giuseppe Gervasi, Placido Bramanti and Rocco Salvatore Calabrò

Abstract

Behavioral disturbances and sexual dysfunctions are common in neurodegenerative disorders. Inappropriate sexual behaviors (ISB) should be seen as a part of the symptom cluster of behavioral disturbances associated with dementia, which are disruptive, distressing, and impair the care of the patient. Sexual disorders, especially loss of libido, are very common in male individuals with Parkinson's Disease, and are suggested to have a multifactorial aetiology, including central and autonomic dysfunction, motor impairment, reduced self-esteem, and psychiatric comorbidity like anxiety and depression.

Sexual Dysfunction in Dementia

Alzheimer disease (AD), a neurodegenerative disease predominantly affecting associative brain regions such as medial temporal, posterior cingulate, lateral temporal, parietal and frontal cortices [1-3], is clinically characterized by a progressive decline in memory and higher cognitive functions. AD patients are mainly impaired in controlled cognitive processes such as explicit memory recall [4], and they frequently rely on familiarity-based processes, allowing them to perform routine (automatic) activities [5-7]. Moreover, personality changes and impaired judgment are typically observed in the disease [8].

AD is the most common form of dementia affecting about 5% of 65 years older and 20% of 85 years older people, and followed by vascular dementia and Lewy body disease. Other less common causes of dementia are Parkinson's disease, alcohol abuse, normal pressure

hydrocephalus, HIV infection, hypothyroidism, and deficiencies of Vitamin B12 and folic acid.

Interestingly, while behavioral disturbances are seen in more than 80% of patients suffering from these disorders, sexually inappropriate behaviors are relatively uncommon causing immense distress to patients and their caregivers.

Sexuality is not only associated with procreation or sexual intercourse, but also includes tenderness, warmth, emotion, passion, and touching, which are all important for the psycho-physical well being of the elderly.

Although general population has historically held vague assumptions and myths concerning sexual issues and practices of the older people, several studies have highlighted how they experience sexual interest and activity [9-12]. Some authors have debated on the right of the elderly to have a regular sexual live indicating that institutions should not allow unmarried older people to have sexual relations or masturbation [13]. In recent years, elderly's quality of live is growing in importance among the general population although sexuality of older people is still marginalised in society [14]. Health professional attitude toward sex issues of elderly is predominantly passive and conservative [15,16], since institutionalized individuals with dementia are typically unable to properly manage their sexual needs [17]. Moreover, caregivers often have a more conservative and limiting attitude toward AD-patients than toward those with higher cognitive status [18,19]. Nevertheless, sexuality is still important in elderly people as well as in the young, but a frequently raised question is: should two demented persons or one demented with a non-demented person be allowed to engage in a sexual relationship? The answer is still under debate, but use the safety-first rule. However, if the patients present a normal cognitive functioning and it is competent to understand a relationship, there is no resistance to let them form such relationship. However, individual's awareness about the relationship, the presence or absence of coercion, moral values, ability to prevent abuse, and psychological aspects of entering and terminating relationships should be always evaluated.

The most frequent sexual disorder in AD-patients is hypersexuality or inappropriate sexual behavior. Many authors refer to these altered behaviors using the following two definitions: [1] overt acts associated with increased libido; [2] persistent, uninhibited, sexual behaviors directed at oneself or other people. Sexual altered behaviors are often verbal and/or physical acts with sexual meaning or intent. Patients could present with increased libido, change in orientation, sexual comments, excessive hugging/kissing, preoccupation with sex, masturbation in public, grabbing at the genitals and/or breasts of other residents or staff, sexual hallucinations, delusions of spousal infidelity, attempting to seduce other residents or staff, chasing other residents for sexual purposes, exposing one's genitals in public, and disrobing in public. Indeed, some behaviors are thought to be inappropriate because they are performed publicly. Moreover, even when inappropriate sexual behavior is not so bouncy, it can be profoundly disruptive to caregivers and other residents in assisted living and skilled nursing facilities [20-21].

It has been shown that over 2/3 patients with dementia will have behavioral disturbances at any one point in time and that 1/3 of outpatients with dementia and 4/5 of the patients living in long-term care facilities have behavioral disturbance [22,23]. Interestingly, behavioral disturbances can lead to increased morbidity, greater health care resource utilization, and premature institutionalization [24].

Nevertheless, epidemiological research regarding inappropriate sexual behaviors in elderly is limited. The best estimate is that 7% to 25% of demented patients exhibit altered sexual behaviors, which are more commonly found in men, although the exact sex ratios are not clear [25].

The brain systems implicated in the neurobiology of inappropriate sexual behaviors are the frontal lobes, the temporo-limbic system, the striatum, and the hypothalamus. Each system is thought to work differently from the other, and we could predict the type of the abnormal behaviors associated with them.

The most well studied of all the brain systems is *frontal lobe* by far. Its dysfunction is commonly seen in dementias, multiple sclerosis, and tumors determining disinhibition rather than hypersexuality more frequently [26-28].

Animal studies have shown that sexual behaviors are also mediated through the *temporo-limbic system*. In humans, bilateral lesions of the temporal lobes result in Kluver-Bucy syndrome, which has been well described elsewhere in this book. Hypersexual behaviors have also been reported after temporal lobe strokes, tumors, and epilepsy. Altered sexual behaviors is more frequent after right-side temporal lesions then left-side as right lobe modulates emotion and the understanding of the affect associated with sexual arousal [29-35].

When lesions of the *corticostriatal circuits* occur, AD patients could present obsessive-compulsive behaviors. Similar behaviors can be seen in Huntington's disease, Wilson's disease, and Tourette's syndrome [36-40].

Lesions involving the hypothalamus can lead to an increase in sexual behaviors; for example, Kleine-Levin syndrome is determined by bilateral hypothalamic dysfunction. Lesions to the right hypothalamus and periventricular area can cause manic symptoms including increased sexual drive [34,41].

Anamnesis with a thorough sexual history is the main part of the assessment in sexology. When the patient is severely impaired, caregivers or family members could give accurate information to clinician. It must be ensured that these behaviors are really sexual and inappropriate and do not represent a desire for closeness or comfort. It is also common for caregivers and the staff at nursing homes to misinterpret some of these behaviors as being sexually disinhibited. History-taking should be followed by a good mental status and physical examination. Laboratory data and neuroimaging examination have to be obtained to rule out delirium. Neuropsychological testing may help in evaluating the patient's level of cognitive functioning and in understanding his or her deficits. It is important to have an open discussion about these behaviors, exploring distress they can cause and how it should be handled. The open communication and a prompt intervention are the keys to success [42-43].

Poor studies have systematically reviewed the treatment of altered sexual behaviors in patients with AD. The choice of treatment depends upon the urgency of the situation, the types of behaviors, and the underlying medical conditions of the patient. Both non-pharmacological and pharmacological treatments have been found to be effective.

When behaviors are due to certain misinterpreted social cues, then modification of these cues usually leads to a reduction at inappropriate behaviors. The most useful non-pharmacological treatments for those behaviors are the following [45-48]:

- *Behavior modification*. Explanation to the patient of the unacceptable nature of behaviors is advisable. Confrontation has to be avoided because it may cause excessive guilt or shame, while ignoring these behaviors could reinforce them.

Distraction with an adequate social activity may be a very useful technique for some of the patients. In nursing homes, single rooms and provision for conjugal or home visits may help reduce the frequency of such behaviors by satisfying the patient's normal sexual drive. For those patients who are already exhibiting inappropriate behaviors, avoidance of over stimulating television or radio programs is helpful. Trousers that open in the back or that are without zippers may be helpful in exhibitionist patient.

- *Supportive psychotherapy*. This modality of treatment is more important for partners of AD patients, which often need reassurance about the nature of these behaviors, which are mostly due to the illness and not a reflection of their relationship. It may also be useful to reframe their partner's sexual requests as calls for closeness and reassurance.
- *Changing the attitudes of the family, caregivers, and staff in the nursing homes*. The care of patients with dementia at home or at a nursing home demands a high degree of technical and interpersonal skills. Caregivers are often caught between moral norms, a person's rights, and providing appropriate cares for their patients. This can lead to confusion, anger, denial, helplessness, and sometimes ambivalence and apathy. Suitable sex-education programs for the family, the caregivers, and the staff at the nursing homes can add to the quality of life of a demented person. The need for normal sexual expression while preventing inappropriate sexual behaviors should be emphasized. Three separate studies have demonstrated that greater knowledge of sexuality and aging is associated with a more permissive attitude.

Medications should only be used when all other treatment methods have failed, following the general rule of starting at a low dose and titrating slowly. Benzodiazepines are not advisable in these patients because can cause disinhibition. The classes of medications that have been found to be useful in the treatment of these behaviors include selective serotonin reuptake inhibitors (SSRIs) antidepressants, antipsychotics, and hormonal agents, along with cimetidine and pindolol.

- Antidepressants. The SSRIs are found to be the best medications to decrease inappropriate behaviors. They present antiobsessional and antilibidinal effects with a high safety in overdose (49,50). Moreover, they tend to decrease sex hormone–induced aggressive behaviors and have an added benefit of treating comorbid depression and anxiety disorders [51]. The common side effects of these drugs are gastrointestinal disturbances, headache, insomnia, and other possible sexual dysfunctions. Only cases about the use of SSRI as treatment of these altered behaviors have been reported. Therapeutical dose of paroxetine is 20 mg daily with an effect seen within 1 week and sustained at 3 –month follow-up. Moreover, citalopram (20 mg daily) is thought to be more effective than paroxetine, thanks to higher selectivity on serotonine reuptake inhibition. Also tricyclic antidepressants, such as clomipramine (at a dose of 150 to 200 mg daily), are found to be effective in the treatment of inappropriate sexual behavior in patients with dementia and exhibitionism [52-54]

- Antipsychotics. The use of antipsychotics as treatment of abnormal sexual behaviors in AD-patients is confirmed only by clinical evidence. To date, no randomized clinical trials have been made to test their efficacy and safety. Their action seems to be related to the dopamine-blocking effect. Atypical antipsychotics are more used in clinical practice rather than typical ones, because of their better tolerance in the elderly. In a case report, an 85-year-old man affected by dementia and Parkinson the altered sexual behavior [54-56].
- Trazodone. Cases of patients with dementia and inappropriate sexual behaviors responding to trazodone, after antipsychotic and benzodiazepine failure, have been described. The main side effects of trazodone, a presynaptic reuptake inhibitor and a mild postreceptor agonist of serotonin, are headache, dry mouth, sedation, orthostatic hypotension, and weight gain. Priapism is a rare complication and seems to be due to the α-2 blocking effect of the drug; when priapism occurs, intracavernous injection of epinephrine may be useful as emergency treatment [57].
- Antiandrogens. The most common antiandrogens are medroxyprogesterone acetate (MPA) and cyproterone acetate (CPA). They act on the reduction in serum testosterone level, which is thought to impair sexual functioning, so to eliminate the inappropriate behaviors. MPA is a progesterone-like molecule that inhibits the levels of pituitary luteinizing hormone (LH) and follicle stimulating hormone (FSH) with a reduction in testosterone blood level. The major side effects are sedation, increased appetite, weight gain, fatigue, loss of body hair, hot and cold flashes, mild diabetes, decreased ejaculatory volume, and symptoms of depression. In 1986, Cooper et al reported 4 male nursing home patients with dementia and inappropriate behaviors. MPA was administered at the dosage of 300mg intramuscularly per week for 1 year with a reduction of undesirable sexual activities within 10 to 14 days. The mean serum levels of testosterone and LH were reduced by 90% and 60%, respectively, after 28 days, but returned to pre-treatment levels within 4 weeks after the end of the trial. At 1-year follow-up, 3 of the 4 patients were free of the inappropriate behaviors, with the forth patient presenting just some inappropriate behaviors. The investigators suggested that the effect of the drug was not only due to the reduction of the testosterone but also to its inhibitory effect on the hypothalamic neurons [58]. To our knowledge, there is no evidence of the use of CPA for hypersexuality in men. Only two case-reports of women with increased sexual behavior or compulsive masturbation have reported so far, with positive results [59].
- Estrogens. The common estrogens used in clinical practice are diethylstilbestrol (DES) and conjugated estrogen. These medications act on LH and FSH secretion reducing testosterone production. Common side effects include fluid retention, nausea, vomiting, impotence, and gynecomastia. Thromboembolic episodes and increased cardiovascular events are common in patients affected by prostate cancer and treated with DES [60]. A marked improvement in sexual abnormalities has been demonstrated in 38 out of 39 patients with dementia treated with oral estrogens or with transdermal estrogen patches [61].
- Gonadotropin-releasing hormone analogs. These medications suppress testosterone production by stimulating the secretion of pituitary LH and FSH, leading to increased

estrogen production and decreased testosterone levels. Leuprolide acetate is the common gonadotropin-releasing hormone (GnRH) analog used in clinical practice. Common side effects include hot flashes, erectile dysfunction, decreased libido, and irritation at the injection sites [62,63]. Opportunity of using these agents for the treatment of hypersexuality in elderly is still under debate. To the best of our knowledge, only two demented patients with hypersexuality, successfully treated with leuprolide, have been reported. . Problems with this drug include the inability of the subject to give informed consent, its particular side-effect profile and the ethical issue on its potential "chemical castration" [64].

- Cimetidine. Cimetidine is an H-2 receptor antagonist with antiandrogen effects. In a retrospective study of 17 men and 3 women with various inappropriate behaviors, 14 had a good response to cimetidine at dose of 600 to 1600 mg daily. Common side effects were nausea, arthralgia, and headaches [65].
- Pindolol. Pindolol is a β-adrenergic blockers, which seems to reduce inappropriate sexual behaviors, agitation and aggression by decreasing adrenergic drive. Nevertheless, only a 75-year-old demented man with aggressive and hypersexual behaviors responding to of 40 mg/daily of pindolol has been described so far. Time to response was 2 weeks. Common side effects of pindolol are fatigue and hypotension [66].
- Mood Stabilizers, Cholinesterase Inhibitors (donezepil, rivastigmine, galantamine) and N-methyl D-aspartate Receptor Antagonist (NMDA) are commonly used in clinical practice as treatment of patients with cognitive impairment. Although there are no clinical evidence on the efficacy and safety of these agents on hypersexuality in AD-patients, they are thought to reduce altered behavior by improving cognitive function [67-70]

Dementia is a public health problem, which is growing in importance. Behavioral problems in these subjects are very common, are considered a major source of distress and, furthermore, they represent one of the main causes of demented patient hospitalization into skilled nursing facilities.

Although inappropriate sexual behaviors in patients with dementia are not as common as other behavioral disturbances, they represent an extremely distressing and often underweighted symptom.

Early detection, prevention and a proper treatment of altered sexual behavior will reduce undue suffering to both the patients and their caregivers, as well as improve the quality of life for all those affected.

References

[1] R.L. Buckner, A.Z. Snyder, B.J. Shannon, G. La Rossa, R. Sachs, A.F. Fotenos, Y.I. Sheline, W.E. Klunk, C.A. Mathis, J.C. Morris and M.A. Mintun, Molecular, structural, and functional characterization of Alzheimer's disease: evidence for a relationship between default activity, amyloid, and memory, J. Neurosci. 2005; 25: 7709–7717.

[2] E. Salmon, S. Lespagnard, P. Marique, K. Herhol, D. Perani, V. Holthoff, E. Kalbe, D. Anchisi, S. Adam and G. Garraux, Cerebral metabolic correlates of four dementia scales in Alzheimer's disease, J. Neurol.2005; 252283–290.

[3] E. Salmon, P. Ruby, D. Perani, E. Kalbe, S. Laureys, S. Adam and F. Collette, Two aspects of impaired consciousness in Alzheimer's disease, Prog. Brain Res.2005; 150: 287–298.

[4] S. Adam, M. Van der Linden, F. Collette, L. Lemauvais and E. Salmon, Further exploration of controlled and automatic memory processes in early Alzheimer's disease, Neuropsychology. 2005; 19: 420–427.

[5] C. Fabrigoule, I. Rouch, A. Taberly, L. Letenneur, D. Commenges, J.M. Mazaux, J.M. Orgogozo and J.F. Dartigues, Cognitive process in preclinical phase of dementia, Brain. 1998; 121:135–141.

[6] G. Dalla Barba, Recognition memory and recollective experience in Alzheimer's disease, Memory.1997; 5: 657–672.

[7] C.E. Westerberg, K.A. Paller, S. Weintraub, M.M. Mesulam, J.S. Holdstock, A.R. Mayes and P.J. Reber, When memory does not fail: familiarity-based recognition in mild cognitive impairment and Alzheimer's disease, Neuropsychology. 2006; 20:193–205.

[8] J.L. Cummings, M. Mega, K. Gray, S. Rosenberg-Thompson, D.A. Carusi and J. Gornbein, The neuropsychiatric inventory: comprehensive assessment of psychopathology in dementia, Neurology 1994; 44: 2308–2314.

[9] Hsieh YH. Sexual problem of the aged. Formosan Journal of Sexology 1995; 1: 99–103.

[10] Helgason AR, Adolfsson J, Dickman P, Arver S, Fredrikson M, Göthberg M, Steineck G. Sexual desire, erection, orgasm and ejaculatory functions and their importance to elderly Swedish men: a population-based study. Age Ageing. 1996;25:285-91.

[11] Bortz WM 2nd, Wallace DH. Physical fitness West J Med. 1999;170:167-9.

[12] Weinberg JS. Human Sexuality and spinal cord injury. Nurs Clin North Am. 1982;17:407-19.

[13] Huang TM. Sexual knowledge and attitude toward elderly in Chinese people 1995; 1, 104–113

[14] Bouman WP, Arcelus J and Benbow SM. Nottingham study of sexuality and ageing. Attitudes regarding sexuality and older people: a review of the literature. Sexual and Relationship Therapy 2006: 21, 149–161.

[15] Chin IC (2004) Factors Related to Nurses' Attitude toward Sexual Behaviors among the Elderly Living in Long-term Care institutions. Unpublished master's dissertation, Shu-Te University, Kaohsiung County.

[16] Gott M, Hinchliff SandGalena E. General practitioner attitudes to discussing sexual health issues with old people. Social Science and Medicine. 2004; 58: 2093–2103.

[17] Kamel HK, Hajjar RR. Sexuality in the nursing home, part 2: managing abnormal behavior—legal and ethical issues. J Am Med Dir Assoc. 2004;5:S49-S52.

[18] Holmes D, Reingold J and Teresi J. Sexual expression and dementia. Views of caregivers: a pilot study. International Journal of Geriatric Psychiatry. 1997; 12, 695–701.

[19] Archibald CA (1998) Sexuality, dementia and residential care: managers report and response. Health and Social in the Community 6, 95–101.

[20] Kuhn DR, Greiner D, Arseneau L. Addressing hypersexuality in Alzheimer's disease. J Gerontol Nurs. 1998;24: 44-50.
[21] Higgins A, Barker P, Begley CM. Hypersexuality and dementia: Dealing with inappropriate sexual expression. BrJ Nurs. 2004-2005;13:1330-1334.
[22] Lyketsos CG, Steinberg M, Tschanz JT, Norton MC, Steffens DC, Breitner JC. Mental and behavioral disturbances in dementia: findings from Cache County Study on Memory and Aging. Am J Psychiatry. 2000;157:708-714.
[23] Margallo-Lana M, Swann A, O'Brien J, et al. Prevalence and pharmacological management of behavioral and psychological symptoms amongst dementia sufferers living in care environments. Int J Geriatr Psychiatry. 2001;16:39-44.
[24] Finkel SI, Costa e Silva J, Cohen G, Miller S, Sartorius N. Behavioral and psychological symptoms of dementia: a consensus statement on current knowledge and implication for research and treatment. Int Psychogeriatr. 1996;8(3 suppl):497-500.
[25] Levitsky AM, Owens NJ. Pharmacological treatment of hypersexuality and paraphilias in nursing home residents. J Am Geriatr Soc. 1999;47:231-234.
[26] Potocnick F. Successful treatment of hypersexuality in AIDS dementia with cyproterone acetate. S Afr Med J. 1992;81: 433-434.
[27] Huws R, Shubsachs AP,Taylor PJ. Hypersexuality, fetishism and multiple sclerosis. Br J Psychiatry. 1991;158:280-281.
[28] Cooper AJ. Medroxyprogesterone acetate (MPA) treatment of sexual acting out in men suffering from dementia. J Clin Psychiatry. 1987;48:368-370.
[29] Persinger MA. Maintained hypersexuality between male rats following chronically induced limbic seizures: implications for bisexuality in complex partial seizures. Psychol Rep. 1994;74:647-652.
[30] Lilly R, Cummings JL, Benson DF, Frankle M. The human Kluver-Bucy syndrome. Neurology. 1983;33:1141-1145.
[31] Monga TN, Monga M, Raina MS, ardjasudarma M. Hypersexuality in stroke. Arch Phys Med Rehabil. 1986;67:415-417.
[32] Blustein J, Seeman MV. Brain tumor presenting as functional psychiatric disturbance. Can Psychiatr Assoc J. 1972;17:S59-S63.
[33] Bear DM, Fedio P. Quantitative analysis of interictal behaviorin temporal lobe epilepsy. Arch Neurol. 1977;34:454-467.
[34] Miller BL, Cummings JL, McIntyre H, Ebers G, Grode M. Hypersexuality or altered sexual preference following brain injury. J Neurol neurosurg Psychiatry. 1986;49:867-873.
[35] Mendez MF, Chow T, Ringman J, Twitchell G, Hinkin CH. Pedophilia and temporal lobe Disturbance. J Neuropsychiatry Clin Neurosci. 2000;12:71-76.
[36] Janati A. Kluver-Bucy syndrome in Huntington's chorea. J NervMent Dis. 1985;173:632-635.
[37] Comings DE, Comings BG. A case of familial exhibitionism in Tourette's syndrome successfully treated with haloperidol. Am J Psychiatry. 1982;139:913-5.
[38] Akil M, Brewer GJ. Psychiatric and behavioral abnormalities in Wilson's disease. Adv Neurol. 1995;65:171-178.
[39] Bowers MB Jr, Van Woert M, Davis L. Sexual behaviors during L-dopa treatment for Parkinsonism. Am J Psychiatry. 1971; 127:1691-1693.

[40] Brown E, Brown GM, Kofman O, Quarrington B. Sexual function and affect in parkinsonian men treated with L-dopa. Am J Psychiatry. 1978;135:1552-1555.
[41] McLean PD. Special award lecture: new findings on brain function and sociosexual behavior. In: Zubin J, Money J, eds. Contemporary Sexual Behaviors: Critical Issues in the 1970s. Baltimore, Md: Johns Hopkins University Press; 1973:53-74.
[42] Kuhn DR, Greiner D, Arseneau L. Addressing hypersexuality inAlzheimer's disease. J Gerontol Nurs. 1998;24:44-50.
[43] Reidenbaugh EM, Zeiss AM, Davies HD, Tinklenberg, JR. Sexual behaviors in men with dementing illness. Clin Geriatr. 1997;5:45-50.
[44] Kamel HK. Sexuality in aging: focus on institutionalized elderly. Annals of long-term care. Clinical Care and Aging. 2001;9: 64-72.
[45] White CB, Catania JA. Psychoeducational interventions for sexuality with the aged, family members of the aged, and people who work with the aged. Int J Aging Hum Dev. 1982;15:121-138.
[46] Aja A, Self D. Alternate methods of changing nursing home staff attitudes towards sexual behavior in the aged. J Sex Educ Ther. 1986;12:37-41.
[47] Sullivan-Miller BH. Dealing with attitudes, preconceived notions. Provider. 1987;13:24-26.
[48] Perilstein RD, Lipper S, Friedman LJ. Three cases of paraphilias responsive to fluoxetine treatment. J Clin Psychiatry. 1991;52:169-170.
[49] McElroy SL, Phillip KA, Keck PE. Obsessive compulsive spectrum disorder. J Clin Psychiatry. 1994;55(suppl):33-51, discussion 52-53.
[50] Black B, Muralee S, Tampi RR. Inappropriate Sexual Behaviors in Dementia. J Geriatr Psychiatry Neurol. 2005; 18:155-162
[51] Guidotti A, Costa E. Can the antidysphoric and anxiolytic profiles of selective serotonin reuptake inhibitors be related to their ability to increase brain 3-alfa and 5-alfa-tetrahydroprogesterone (allopregnelone) availability? Biol Psychiatry. 1998:44:865-873.
[52] Stewart JT, Shin KJ. Paroxetine treatment of sexual disinhibition in dementia. Am J Psychiatry. 1997;154:1474. 44. Raji M, Dongjie L,Wallace D. Sexual aggressiveness in a patient with dementia: sustained clinical response to citalopram. Annals of Long-Term Care. 2000;8:81-83.
[53] Leo RJ, Kim KY. Clomipramine treatment of paraphilias in elderly demented patients. J Geriatr Psychiatry Neurol. 1995; 8:123-124.
[54] Nagaratnam N, Gayagay G. Hypersexuality in nursing care facilities—a Descriptive study. Arch Gerontol Geriatr. 2002;35: 195-203.
[55] Maixner SM, Mellow AM,Tandon R. The efficacy, safety, and tolerability of antipsychotics in the elderly. J Clin Psychiatry. 1999;60(suppl 8):29-41.
[56] Macknight C, Rojas-Fernandez C. Quetiapine for sexually inappropriate behavior in dementia. J Am Geriatr Soc. 2000;48:707.
[57] Simpson DM, Foster D. Improvement in organically disturbed behavior with trazodone treatment. J Clin Psychiatry. 1986; 47:191-193.
[58] Weiner MF, Denke M, Williams K, Guzman R. Intramuscular medroxyprogesterone acetate for sexual aggression in elderly men. Lancet. 1992;339:1121-1121.
[59] Cooper AJ. Progestogens in the treatment of male sex offenders: a review. Can J Psychiatry. 1986;31:73-79.

[60] Mellor CS, Farid NR, Craig DF. Female hypersexuality treated with cyproterone acetate. Am J Psychiatry. 1988;145:1037.
[61] Kyomen HH, Noble KW,Wei JY. The use of estrogen to decrease aggressive physical behavior in elderly men with dementia. J Am Geriatr Soc. 1991;39:1110-1112.
[62] Lothstein LM, Fogg-Waberski J, Reynolds P. Risk management and treatment of sexual disinhibition in geriatric patients. Conn Med. 1997;612:609-618.
[63] Ott BR. Leuprolide treatment of sexual aggression in a patient with dementia and Kluver-Bucy syndrome. Clin Neuropharmacol. 1995;18:443-447.
[64] Rich SS, Ovsiew F. Leuprolide acetate for exhibitionism in Huntington's disease. Mov Dis. 1994;9:353-357.
[65] Wiseman SV, McAuley JW, Freidenberg GR, Freidenberg DL. Hypersexuality in patients with dementia: possible response to cimetidine. Neurology. 2000;54:2024.
[66] Jensen CF. Hypersexual agitation in Alzheimer's disease. J Am Geriatr Soc. 1989;37:917.
[67] Young RC, Gyulai L, Mulsant BH, et al. Pharmacotherapy of bipolar disorder: review and recommendations. Am J Geriatr Psychiatry. 2001;12:342-357.
[68] Lonergan ET, Cameron M, Luxenberg J.Valproate preparation for agitation in dementia. Cochrane Database Syst Rev. 2004;4:CD003945.
[69] Cummings JL. Use of cholinesterase inhibitors in clinical practice: evidence-based recommendations. Am J Geriatr Psychiatry. 2002:11:131-145.
[70] Areosa SA, Sherriff F, McShane R. Memantine for dementia. Cochrane Database Syst Rev. 2005;18:CD003154.

Sexual Dysfunction in Parkinson Disease

Parkinson's Diseases (PD) involves motor system, mental, cognitive and autonomic functions, and is clinically characterized by motor and non motor impairment. Among the latter, the sexual dysfunction (SD) are frequent, impairing quality of life and welfare, but are often overlooked for various reasons, including: reluctance of patients in dealing with sexual problems, lack of awareness about the possible relationship between PD and SD, omission of sexual anamnesis.

Moreover, another aspect to take into account is the relationship between PD and sexual hormones. Indeed, hormones affect the dopamine system and may have a neuroprotective function and effects on symptoms of the disease with implications for clinical practice. SD in PD can result from alterations in motor, mental or cognitive disease-specific functions and involve both the desire and the sexual arousal. SD is more common in patients with PD compared with controls of the same age and is more common in men than women. It was observed alteration also in excitement [1] because of the interference of motor impairments and other non motor disorders on sexual activity (sialorrhea, seborrhea, bradykinesia, akinesia, etc.). Motor disorders of PD (bradykinesia, rigidity, tremor, immobility in bed, difficulty in movements of the fingers and hands) can alter the physical contact between partners and make sexual intercourse very difficult. This leads the patient to have a more passive role with the sexual partners and to require a patient with a more active role. Some

events such as sweating, drooling, disorders of posture, and tremor make patients less attractive, while hypomimia could be interpreted by the partner as a lack of feeling or desire.

Sleep and nocturnal disturbances, such as REM behaviour disorders, can lead to separation of the bed, which further decrease the opportunities for intimate contact. Moreover, the presence of depression, anxiety, apathy, often present, may also lead to reduced function and sexual satisfaction. Finally, several drugs can cause either hyposexuality or hypersexuality. For example, libido seems to rise after dopaminergic therapy [2]: L-Dopa in 8% of patients is used to restore sexual activity and in 1% of patients induces hypersexuality [3]; the dopamine agonists may induce hypersexuality in 3% of patients [4], and apomorphine and ropinirole probably have an effect on stimulation of D2 receptors of preoptic area with an increase of oxytocin at the lumbosacral spinal level, which cause erectogenic stimuli. PD can interfere with sexuality through a more specific mechanism. Indeed, the dopaminergic system (meso-diencephalon and spinal cord) is crucial in sexual desire and excitement [5]: dopamine acts on preoptic area, medial accumbens nucleus, and spinal cord [6]. Alterations of the prefrontal cortex (whose function is modulated by dopamine) are frequently associated with apathy syndrome, characterized by lack of motivation that involves sexual desire, leading to deficiency of excitement and difficulty achieving orgasm [7].

The degeneration of dopaminergic neurons also determines the impairment of these neural systems. Finally, neuropathological data suggest that brain structures involved in sexual behaviour are also early affected in PD. Actually there is an increasing body of evidence supporting the existence of lateralized brain asymmetries in the regulation of neuroendocrine, reproductive and sexual functions [8]. For instance, there is more gonadotropin-releasing hormone (GnRH) in the right ventromedial hypothalamus than in the left in experimental models [8]. The secretion of this hormone is stimulated by dopamine which, conversely, stimulates the secretion of luteinizing hormone (LH). LH regulates the synthesis of steroids hormones, such as testosterone. This hormone, either directly or through its metabolic products, has inhibitory effects on the secretion and release of GnRH and it directly inhibits the secretion and release of gonadotropins. Prolactin, which is inhibited by dopamine, is also a potent inhibitor of GnRH secretion and then indirectly inhibits LH and testosterone secretion. A dopaminergic deficit has been demonstrated in the hypothalamus of PD patients [9]. Thus, PD and dopaminergic medication may influence hypothalamic and pituitary function. However, PD patients do not seem to differ from healthy elderly in gonadotropic hormones and testosterone levels [10]. Unfortunately, the few studies that assessed endocrine functioning in PD have not considered disease asymmetry and thus neglected the relevance of neuroendocrine asymmetry. Nevertheless, alterations in the concentrations of serum testosterone can be considered a possible cause of SD in patients with PD. A reduced availability of testosterone is found in 20-25% of PD and it can cause depression, fatigue, anxiety, lack of energy and decreased libido [11], which may be resolved with adequate hormone replacement therapy. In PD patients there is a significant inverse correlation between free testosterone levels and apathy, although there are still controversies on the practical relevance of this issue [12]. It was reported, however, that testosterone therapy in patients with reduced serum levels improves motor and non-motor disorders. Indeed, testosterone can improve writing, tremor, stride length, the ability to cut food, for the latter, testosterone may improve depression, anxiety, libido, SD, all disorders that are often resistant to antiparkinsonian therapy [10].

Cognitive functioning, in spite of its close relationship with age and mood, was also associated with SD. Of note, the right prefrontal cortex is particularly important for the emotional responses of sexuality [13]. Furthermore, changes in androgen levels in older men modulate, at least in part, the cognitive changes of aging [14]. Fatigue is an additional problem in PD and it is frequently related to major depression, sleep disorder, cognitive impairment, comorbidities, and testosterone deficiency [15].SD in male PD are erectile dysfunction, sexual dissatisfaction, premature ejaculation, anorgasmia. Other issues of sexuality are hypersexuality and paraphilias [16]. Almost all the partners of young patients (<60 years) are sexually dissatisfied [17]. It is estimated that about 60% of patients report SD. It is interesting to note that erectile dysfunction is associated with an increased risk of developing PD; indeed, the presence of erectile dysfunction, anosmia and constipation can help identifying those at risk of developing PD [18]. Erectile dysfunction is certainly one of the most common non motor symptoms in PD, but it also easily diagnosed and is currently well controlled with therapy [19]. Several therapeutic aids are useful for treatment. The first is the use of dopamine agonists. If there is no adequate effectiveness, inhibitors of phosphodiesterase type 5 (tadalafil, vardenafil, sildenafil) are extremely effective. Phosphodiesterase type 5 (PDE 5) enzymes are highly concentrated at the level of visceral smooth muscle where reduce cyclic adenosine monophosphate guanosine (cGMP), the second messenger of nitric oxide, involved in the relaxation of vascular smooth muscle [19]. This pathway is essential for vasodilatation in the corpus cavernosum. Sildenafil, tadalafil and vardenafil can sometimes cause mild and transient side effects: headache, flushing, dyspepsia, rhinitis, abnormal vision, back pain and myalgia. Apomorphine is indicated in patients with orthostatic hypotension in which PDE inhibitors are contraindicated [20]. Hypersexuality is one of the possible manifestations of the disorder of impulse control, which affects about 5% of PD patients [4]. This dysfunction is more frequent in patients taking dopamine agonists or IMAO-B, in those with a history of mood disorders, anxiety, irritability or aggressiveness, impulsivity, alcohol or drug abuse [4]. When hypersexuality is associated with mild cognitive impairment, the use of acetylcholinesterase inhibitors may be therapeutical. PD-related SD, which has been suggested as a result of central and autonomic dysfunction compounded by defective motor skills, reduces self-esteem so that comorbid psychiatric states like anxiety and depression are rather common in these patients [16]. However, it has received scant attention both in clinical context and in research. SD in PD is often underrecognized and undertreated. However, some studies have shown that, in both genders, sexual difficulties in getting aroused and decreased desire are highly frequent in PD. In addition, decreased sexual desire in patients with PD correlates with reduced general satisfaction from life. Although erectile dysfunction and premature ejaculation have been pointed out as the main causes of higher levels of sexual dissatisfaction, men with PD may have lack of drive and interest in sex even thought they are still potent. Studies about SD are incomplete and contradictory [16]. Some authors have already considered some variables when assessing SD in PD such as age, stage and disease duration and severity, impact in activities of daily living, and quality of life. However, many variables, such as psychiatric disorders, cognition, fatigue, apathy, sleep disorders, drug therapy, and personal relationships have been neglected. Data regarding SD in PD are scarce; nevertheless, the prevalence of sexual problems in PD seems to be higher than in the general population. Lindau et al. have recently published the results of a community-based survey assessing sexual life in more than 3,000 elderly [21]. The most important factors in the development of SD were aging and female gender. Among women, low desire was the

most prevalent sexual problem, while erectile dysfunction was the most prevalent one among men. In PD, decreased interest in sex was associated with aging and female gender, too. However, depression seems to be the most important predictor of loss libido. The relationship between depressive disorders and sexual disorders is well established. The largest study assessing the prevalence of SD in depressed patients showed that 52.8% of untreated patients reported decreased libido [22]. Lipe et al [23] reported a study in which the sexual function of a group of male Parkinson's disease patients was compared with a group of patients with arthritis. Sexual problems were found to increase in relation to disease severity and depression in both groups; moreover, the two groups were similar in all measured aspects of sexual functioning, with the exception of more arousal dysfunctions in the PD group. Interestingly, a recent study has reported hypersexuality as a complication of levodopa treatment in PD [24]. The general lack of professionals' interest in sexual function in Parkinson's disease may relate to two main assumptions, neither of which is warranted. First, Parkinson's disease is not generally assumed to be associated with physiological dysfunction or neuronal damage that would interfere with the sexual response. Autonomic dysfunction affecting the urogenital system is, however, found in some patients with idiopathic Parkinson's disease, whereas in patients with Parkinsonism, especially in multiple system atrophy, such autonomic dysfunction may be the main problem. Second, there may be an implicit assumption that patients with Parkinson's disease, being generally middle-aged or elderly, are not interested or have a diminishing interest in sex. While the frequency of sexual intercourse may diminish with age, this does not mean that sexuality plays no role in the lives of the elderly. This assumption also ignores the significant proportion of cases with early onset Parkinson's disease who develop the disease in early or mid-adulthood when reduced sexual activity is not the norm. While autonomic nervous system involvement may be a possible cause of primary sexual dysfunction in some patients with Parkinson's disease, many other factors may lead or contribute to secondary sexual dysfunction, either in the patient, their partner or both. The motor symptoms of Parkinson's disease may make the act of sexual intercourse difficult. Fatigue may also play a role. Anti-Parkinsonian medication may have some effect on both libido and the sexual response. The hypersexuality reported in some patients may be a problem, whereas the desire of an increasing in frequency of sexual intercourse is not shared by both partners. Diminishing physical capacity may necessitate the patient taking a more passive role. In addition, because of drug regimes, motor function for many patients is at its best in the morning and worst at night. A shift in the pattern of sexual activity may therefore be desirable to take advantage of the optimum motor status of the patient. Difficulties may develop in couples who do not want to try, or are unwilling to make, such adaptive changes in sexual behaviour, either in its timing, or in the roles played by individual partners. Furthermore, if the patient's movement disorder is disruptive at night, the couple may take sleeping in separate beds or even in separate rooms, thus decreasing the opportunity for spontaneous sexual contact. In conclusion, the disturbance of sexual function in PD is a complex phenomenon resulting from the interaction of several factors: neurodegeneration areas of central and autonomic nervous system involved in sexual function, mental and physical impairment and disability homeostasis generated by the disease, sexual side effects of drug therapy, altered relationship dynamics with their partner, and comorbidities such as dyslipidemia, hypertension, diabetes, hypogonadism and depression.

References

[1] Hobson P, Islam, Roberts S, Adhiyman V, Meara J. The risk of bladder and autonomic dysfunction in a community cohort of Parkinson's disease patients and normal controls. *Parkinsonism Relat. Disord. 2003*;10:67-71.

[2] Yahr MD, Duvoisin RC. Drug therapy *N. Engl. J. Med.* 1972;287:20-4. Review.

[3] Goodwin FK, Murphy DL, Brodie HK, Bunney WE Jr. Levodopa: alterations in behavior. *Clin. Pharmacol. Ther.* 1971;12:383-96.

[4] Weintraub D, Siderowf AD, Potenza MN, Goveas J, Morales KH, Duda JE, Moberg PJ, Stern MB. Association of dopamine *Arch. Neurol.* 2006;63:969-73.

[5] Andersson KE. Pharmacology of penile erection. *Pharmacol. Rev.* 2001;53:417-50.

[6] Fibiger HC, Phillips AG. Mesocorticolimbic dopamine *Ann. N Y Acad. Sci.* 1988;537:206-15.

[7] Everitt BJ. Sexual motivation *Neurosci. Biobehav. Rev.* 1990 Summer;14:217-32.

[8] Gerendai I, Halász B. Asymmetry *News Physiol. Sci.* 2001;16:92-5.

[9] Sandyk R, Iacono RP, Bamford CR. The hypothalamus *Ital. J. Neurol. Sci.* 1987;8:227-34.

[10] Okun MS, McDonald WM, DeLong MR. Refractory nonmotor symptoms *Arch. Neurol.* 2002;59:807-11.

[11] Okun MS, DeLong MR, Hanfelt J, Gearing M, Levey A. Plasma testosterone *Neurology.* 2004;62:411-3.

[12] Kenangil G, Orken DN, Ur E, Forta H, Celik M. The relation of testosterone *Clin. Neurol. Neurosurg*. 2009;111:412-4.

[13] Tiihonen J, Kuikka J, Kupila J, Partanen K, Vainio P, Airaksinen J, Eronen M, Hallikainen T, Paanila J, Kinnunen I, et al. Increase in cerebral blood flow of right prefrontal cortex in man during orgasm. *Neurosci. Lett.* 1994;170:241-3.

[14] Amore M. Partial androgen deficiency and neuropsychiatric symptoms in aging men. *J. Endocrinol. Invest.* 2005;28(11 Suppl Proceedings):49-54.

[15] Friedman JH, Brown RG, Comella C, Garber CE, Krupp LB, Lou JS, Marsh L, Nail L, Shulman L, Taylor CB; Working Group on Fatigue in Parkinson's Disease. Fatigue in Parkinson's disease: a review. Mov. *Disord.* 2007; 22:297-308.

[16] Meco G, Rubino A, Caravona N, Valente M. Sexual dysfunction in Parkinson's disease. Parkinsonism *Relat. Disord.* 2008;14:451-6.

[17] Schulzer M, Mak E, Calne SM. The psychometric properties *Parkinsonism Relat. Disord.* 2003;9:291-4.

[18] Gao X, Chen H, Schwarzschild MA, Glasser DB, Logroscino G, Rimm EB, Ascherio A. Erectile function and risk of Parkinson's disease. *Am. J. Epidemiol.* 2007;166:1446-50.

[19] Papatsoris AG, Deliveliotis C, Singer C, Papapetropoulos S. Erectile dysfunction in Parkinson's disease. *Urology.* 2006 Mar;67(3):447-51.

[20] O'Sullivan JD. Apomorphine as an alternative to sildenafil in Parkinson's disease. *J. Neurol. Neurosurg. Psychiatry.* 2002;72:681.

[21] Lindau ST, Schumm LP, Laumann EO, Levinson W, O'Muircheartaigh CA, Waite LJ. A study of sexuality *N. Engl. J. Med.* 2007; 357:762-74.

[22] Kummer A, Cardoso F, Teixeira AL. Loss of libido *J. Sex. Med*. 2009;6:1024-31.

[23] Lipe H, Longstreth WT, Bird TD, Lind M. Sexuality in Parkinson's disease. *Neurology.* 1989;39(suppl 1):320.

[24] Vogel HP, Schiffter R. Hypersexuality-a complication of dopaminergic therapy in Parkinson's disease. *Pharmacopsychiatrica.* 1983;16:107-10.

In: Male Sexual Dysfunctions in Neurological Diseases… ISBN 978-1-61761-855-0
Editor: Calabrò Rocco Salvatore

Chapter 8

Sexual Dysfunction in Spinal Cord Injury

Concetta Pastura, Gianni D'Aleo, Antonino Levita, and Rocco Salvatore Calabrò

Abstract

Despite advances in the field of medicine, injury to the spinal cord remains a devastating problem. Spinal cord Injury (SCI) often results in permanent neurological deficit and, depending on the level of injury, may leave the patient severely disabled. SCI has a dramatic emotional impact on the patient and his family and represents a high burden to society. Moreover, patients with SCI have a poor quality of life, often worsened by the presence of sexual dysfunction, which is really dramatic especially at a young age.

Introduction

Spinal cord injury can be divided into traumatic injury and non traumatic injury.

Traumatic Spinal Cord Injury

Between 2000 and 2003 the most common causes of SCI were motor vehicle crashes (50,4%), falls (23,8 %), sports (9%), violence (11,2%) and others (5,6 %).

The sports associated to high risk of traumatic SCI are: rock climbing, surfing and diving.

SCI causes incomplete tetraplegia in 34,5% of cases, complete paraplegia in 23,1%, complete tetraplegia in 18,4%, and incomplete paraplegia in 17,5% [1-2] .

In SCI patients reported mortality ranges from 4,4-16,7%) [3] .

In Italy the most common causes of traumatic SCI are: falls 22%, sport 8%, suicide attempts 4%, violence 2%, other 9% [4] .

If we exclude the gunshot wounds, from cuts and/or bullet fragments, the most common cause of traumatic SCI is the result of a force that is applied at distance from the region where the damage occurs, i.e. hyperflexion (determining forward bending of the spine), hyperextension (determining bending backward of the spine), rotation (determining twisting of the spine) and compression (determining crushing of the spine).

The cervical spine and the point of transition between the dorsal and lumbar spine, are the most affected segments, since they are more mobile. Over 2/3 of spinal injury involves C3, C4 and C5 vertebral bodies , with complete spine injury in 20% of cases, 1/3 of spinal injury involving the dorsal and lumbar spine, especially from D1 to D5 and from D1 a L1, with complete spine injury in 39% of cases.

Non Traumatic Spinal Cord Injury

Excluding multiple sclerosis (MS), the most common causes of SCI in the young are: tumors (25%), vascular disease (25%), inflammatory disease (19,5 %) spinal stenosis (18,6%), degenerative central nervous system (CNS) diseases (10 %) and other 7 % (5) (table 1) .

SCI Syndromes

According to the International Standards for Neurological Classification,
SCI can be classified as *tetraplegia* (quadriplegia) if it involves a cervical spinal segment or *paraplegia* if it involves a thoracic, lumbar, or sacral spinal segment. SCI is further identified as being *complete* (absence of all motor or sensory functions at the lowest sacral level) or incomplete (at least some preservation of motor or sensory functions below the level of the injury, including the lowest sacral level).

Complete SCI is a *functional* transection of the spinal cord in which electrical impulses of sensory information going up to the brain, as well as motor information coming down from the brain, are disrupted. It is the complete loss of neural communication across the injury level evidenced by the neurologic examination that establishes a poor prognosis of recovery.

Incomplete spinal cord injuries cover the spectrum from patients that have minimal preservation of distal sacral function to those that are practically normal. Even the more severe incomplete injuries have a significantly better prognosis than a complete SCI.

In the *central cord syndrome*, the patient's upper extremities are neurologically impaired, particularly the hands, but the lower extremities are relatively spared. If severe, the patient may appear to have a complete loss of neurologic function below the level of the injury but maintains bowel and bladder control.

In *anterior spinal syndrome* the patient is weak in all four extremities with loss of pain and temperature sensation in all extremities; however, vibration and position sense (posterior columns) remain intact. This syndrome is thought to be the result of inadequate blood supply from the anterior spinal artery, either occlusion through compression or embolization.

Table 1. Causes of non traumatic SCI

Causes	
Tumors	Extradural Intradural-extramedullary Intramedullary
Vascular disease	Spinal cord ischemia Spinal cord hemorrhage (hematomyelia, subarachnoid, epidural and subdural hemorrhage)
Myelitis (transverse, widespread and disseminated)	Infective (viral, bacterial, protozoal and parasitic) Noninfectious
Stenosis	
Malformation	Chiari malformations (from type I to type IV and acquired) Vascular malformations (epidural, cavernous, complex, arteriovenous malformation, arteriovenous fistula, dural arteriovenous fistula, metameric and disseminated angiomatosis) Syringomyelia Spina bifida (occult and manifest spina bifida such as meningocele and myelomeningocele)
Genetic diseases	Spinocerebellar ataxia Motoneuron diseases Hereditary spastic paraplegia

The posterior columns are spared, because this area is supplied by the paired posterior spinal arteries. In 1850, Brown-Sequard described a *functional hemisection of the cord* that now bears his name, the *Brown-Sequard syndrome*. Clinically, it is characterized by weakness ipsilateral to the injury and controlateral loss of pain and temperature. The anatomic basis for these neurologic findings is that postsynaptic pain and temperature fibers cross in the spinal cord near their point of origin, whereas motor fibers cross in the brainstem. Lesions of one side of the spinal cord interrupt ipsilateral descending motor pathways and contralateral ascending pathways conveying pain and thermal sensations.

Cauda equina, which arises from conus medullaris, supplies the legs as well as bowel, bladder, and genital areas. Lesions of this structure lead to lower extremity weakness and numbness with associated bowel, bladder and sexual function deficiencies [6].

Physiology of the Erection and Ejaculation

Erection

A parasympathetic centre (reflex-activated centre), located in the spinal cord segments S2-4 is the main mediator of erection. The efferents run in the nervi errigentes, but the final pathway is believed to be short adrenergic nerves that release norepinephrine. The afferents transmitting penile sensation run in the pudendal nerve to the sacral centre.

A sympathetic centre, psychologically activated and located in T11-L2, likewise mediates erection through fibres in the hypogastric nerves to the corpora cavernosa.

Erection is sustained by compression of the veins between the expanded corpora and the tunica albuginea. It is the smooth muscle relaxation of the penile arteries and in the corpus cavernosum, which leads to the penile erection. This is a result of parasympathetic/noradrenergic noncholinergic neural pathway activation and simultaneous inhibition of sympathetic outflow.

Ejaculation

The sympathetic nervous system (T11-L2) sends efferent fibers in the hypogastric nerve to vasa deferentia, seminal vesicles and prostatic smooth muscle fibers, and gives rise to the peristalsis necessary for seminal emission i.e. the first phase of ejaculation. Closure of the bladder neck as well is enforced through sympathetic stimulation.

The parasympathetic centre (S2-4) supplies nervi errigentes with efferents to the prostate glands, in part leading to the formation of seminal fluid.

A somatic centre, located in S2-4, with fibers in the pudendal nerve, supplies the bulbospongiosus and ischiocavernous muscles and the muscle of the pelvic floor to bring about the clinic contractions causing the projectile ejaculation with release of semen from the urethra: the second phase of ejaculation. Therefore, if a person has a lesion of this centre, ejaculation is not projectile, but dribbling in nature [7].

Sexual Function in Spinal Cord Lesion Men

Studies on war veterans identified spinal reflex and psychogenic pathways for erection and showed that level and completeness of spinal cord damage determine the extent to which erectile and ejaculatory capacity is affected [8]. Indeed, the impact on sexual functioning depends on the degree of injury and its location on the spinal cord [9,10] .

After SCI involving specific spinal centre, male patients may present erection, ejaculation and fertility dysfunction, while women may experience [11-13] pain with intercourse and inability to reach orgasm [14,15] . Erectile dysfunction is defined as the inability to achieve or maintain an erection sufficient for satisfactory sexual activity [16] .

Guttman [17] distinguished three phases in the pathophysiology of the sexual dysfunction: spinal shock, reflex return and readjustment.

The phase of spinal shock lasts from few hours to several weeks, during which there is a complete or almost complete suppression of reflex activity below the level of the cord lesion. Male genital reflexes (reflex penile erection, bulbocavernosus and scrotal reflexes) are abolished or profoundly depressed; erectile and ejaculatory functions are abolished.

Spinal shock is believed to be due to the sudden interruption of the suprasegmental descending fiber systems that keep the spinal motor neurons in a continuous state of subliminal depolarization [18] . The period of spinal shock is the main reason why it is almost impossible to predict sexual function recovery (including erection and ejaculation) in SCL men within the first weeks after the injury. After this phase, reflex activity and spasticity may appear in the lower extremities, and bladder and bowel function may become reflexogenic. In suprasacral lesions the erection reflex becomes one of the components of the autonomic functions of the isolated cord, taking part in the `mass response'. In fact, it may appear independently of cerebral participation, before the reflex responses of the skeletal muscles are fully developed. Tactile stimuli of varying type and intensity, including stimulation of the glans and around the penis, may result in erection [19] .

Sexual readjustment after injury was closely and positively correlated with willingness to experiment with alternative sexual expressions and young age at injury. Physical and social independence and a high mood level were further positive determinants of sexual adaptation after injury [20] .

Three types of erections after SCL [21,22] have been described. Reflexogenic erection is induced by cutaneous or mucous membrane stimulation from areas below the level of the lesion, thus requiring an intact reflex arc, including S2 - 4. Psychogenic erection is induced by psychic stimulation: visual, auditory, olfactory, as well as dreams, memories, and fantasies. In SCL men with lesions below L2 it is believed to be via the thoracolumbar sympathetic outflow. This erection results only in swelling and lengthening of the penis without rigidity, and therefore, without the possibility of intromission (i.e. impotentia coendi).

Mixed erection may occur when the level of the lesion is below L2 and above S2. The erectile response may differ individually regarding the duration and quality of the erection.

In conclusion, after a complete *high lesion*, psychogenic erections are lost but reflex ones remain. *Lower lesions* (at conus and cauda equina level), reduce erectile capacity. Erotic sensations travel in spinal cord pathways close to the spinothalamic tract (23,24) . Nevertheless, Alexander *et al*. described the ability to experience orgasm in about 38% of men with apparently complete lesions [25] .

Damage to the *cauda equina* is likely to affect both the anterior and posterior sacral pathways that contain somatic and parasympathetic fibers. This can determine both loss of perineal sensation and sexual response and loss of voluntary control of the anal and urethra sphincters. Rees *et al.* [19] observed that out of 36 mostly ambulant men with long-standing cauda equina damage of various etiologies, 35 reported sustained sexual dysfunction, which was moderate or severe in 59%, but only drugly attended to in five cases [28] . The combination of loss of genital sensation and function makes any alleviation of sexual dysfunction in men very difficult [27] .

It has been found that incomplete SCI patients are better in assessing their erectile function than persons with complete lesions [29] . Courtois et al [30] observed, using penile strain gauge and reflexogenic stimulation (masturbation) and psychogenic stimulation (film), that erectile potential was a function of the lesion type and stimulation source.

Erection is more likely to be obtained in incomplete than complete lesions. Individuals with suprasacral lesions with an intact parasympathetic centre, have a higher frequency of erection than individuals with lower lesions [31].

Indeed, in a group of patients with complete and incomplete SCI, Tsuji et al [32] found recovery of erectile function in about 25% within 1 month after injury, in 60 % within 6

months, and in 80% within 1 year; in 5 %, the recovery occurred after 2 years. In those with cervical or thoracic vertebral injury, 30% to 40% regained erectile function within 1 month, and 70% to 80% within 6 months. Only 10% of those with a lumbar vertebral injury recovered erectile function within 1 month and 40% within 6 months.

In addition to having problems with erectile dysfunction, ejaculatory function may be compromised in SCI because of impairment in the coordinated neurologic impulses between the sympathetic, parasympathetic and somatic nervous systems [33,34] . Ejaculation and orgasm are likely to occur simultaneously, although a number of men with SCI achieve orgasm without ejaculation [26] . Men with incomplete SCI are more likely to achieve simultaneous orgasm than men with any other patterns of SCI [34,35] .

After a complete spinal-cord injury, only 4% of men with high lesions and 18% of men with lower lesions are able to ejaculate [8]. Poor sperm quality after spinal-cord injury is a further confounding factor. Vibrostimulation or electroejaculation from transrectal stimulation of the prostatic nerve plexus allows sperm retrieve for assisted reproductive techniques [26,27] .

Male infertility associated with SCI occurs from a combination of erectile dysfunction and ejaculatory failure. In the acute phase of SCI, semen quality is normal (6-12 days post-injury) but in the following weeks, sperm motility and viability declines [34] .

Other factors that contribute to infertility include frequent urinary tract infections, impaired scrotal thermoregulation and retrograde ejaculation [37,38]

Sexual dysfunction has physiologic and psychological causes and its effect is influenced by the patient's age, gender, culture and comorbid medical conditions. Changes in physical appearance, limited sexual positioning, autonomic dysreflexia, urinary and bowel incontinence, spasticity, neuropathic pain and alteration of the thermoregulation, are factors that negatively impact sexual arousal and activity [11] .

Urine leakage is possible during sexual intercourse; moreover, urine odor and external drainage devices may negatively impact desire, libido and sexual arousal. SCI patient may experience bowel incontinence and flatulence during sexual activity.

The possibility of autonomic dysreflexia affecting bladder and bowel function, cardiovascular control and temperature regulation may diminish willingness to engage in sexual activity.

The appearance and texture of the skin and the risk for skin breakdown not only limit sexual positioning but greatly affect comfort with body [39] . The reduced capability to balance and support the body, imposes limits on sexual positioning and movements of the pelvis during intercourse. In addition, sudden muscle spasms can interrupt sexual activity and restrict positioning [39,40,41] .

Nursing intervention includes fostering two-way and open communication on sexual intimacy issues between SCI patients and their partners. Identifying new erogenous zones and sexual positions by exploration and communication between partners is critical to returning to a fulfilling sexual activity after SCI. Patients will not be able to use all of the coital positions they used before SCI. It is only through personal exploration and communication that new coital positions will be identified [11] .

Recent literature has provided insight into the psychological impact of SCI, specifically evaluating sexual satisfaction and predictors of positive outcome [39,42, 43] .

Sexual satisfaction, desire and fulfillment are greater in patients who are engaged in a strong emotional relationship with good communication and who are open to sexual

experimentation, and when the patient perceives that his/her partner enjoys the sexual aspects of their relationship [11] .

Improving sexual function remains a priority for people living with SCI and the current means of enhancing sexual ability are still deemed unsatisfactory in regard to improving quality of life (QoL) [41, 43, 44,45, 46, 47, 48].

Drugs for Spinal Cord Injury and Sexual Dysfunction

Sixty per cent of people with spinal cord injury (SCI) show spasticity; this is the major secondary medical problem and is responsible for medical interventions or hospitalization [49] .

Severe spasticity can have a profound adverse impact on the patient's ability to cope with everyday activities and, thus, on the quality of life [50] .

Spasticity can be treated with oral medication (such as baclofen, tizanidine, clonidine), injection of botulinum toxin for localized spasms or intrathecal administration of baclofen or clonidine [51] .

The most used drug to control spasticity is baclofen (Beta-[4-clorofenil] GABA), a muscle relaxant drug, derivative of the neurotransmitter gamma aminobutyric acid (GABA).

Chronic intrathecal baclofen infusion in patients with spinal cord lesions caused a reversible decrease of erection rigidity and/or reduced duration and impairment of ejaculation (Denys et al, 1998). This observation led to the introduction of oral baclofen in the treatment of refractory and recurrent idiopathic priapism [52-54] .

To the best of our knowledge, no data are available about the utility of intrathecal baclofen for the treatment of otherwise refractory priapism that may occur in patients with spinal spasticity. We have recently reported [55] a 41-year-old male patient who sustained a severe traumatic spinal cord injury in a motor vehicle accident. On clinical examination he presented with tetraplegia due to a C3-C4 lesion with a herniated disc and compression of the dural sac.

One month after discectomy, the patient, developed a gradual increase of spasticity mild erectile dysfunction, which enabled him to have only occasionally satisfactory sexual intercourse, and priapism episodes.

Since high oral baclofen resulted only in a mild improvement of his spasticity and priapism with important side effects, an intrathecal pump system (Medtronic Synchromed EL, Minneapolis, MN) was implanted, leading to a decrease of spasticity, absence of priapism episodes, and improvement of urge incontinence.

At 5 years follow up, the patient experienced a further episode of priapism, only when he missed a pomp refilling.

Priapism is a persistent penile erection that is unrelated to sexual stimulation. Subtypes include ischemic, non-ischemic, and intermittent (stuttering) priapism. Treatment of priapism includes systemic drugs (*e.g.*, antiandrogen hormonal agents), baclofen, digoxin, and terbutaline); self-injection of sympathomimetic agents (*e.g.*, phenylephrine) into the corpus cavernosum; and as a last resort a penile prosthesis [56].

Studies in rats and humans suggest that baclofen, a GABAB receptor agonist, inhibits penile erection and ejaculation [57,58] .

Intrathecal injections of baclofen (0.2, 0.4, or 0.8 ug) into the subarachnoid space of the lumbosacral spinal cord (L5-S1) resulted in a dose-related decrease of the number of animals responding in a penile reflex test [58]

Baclofen doses of 0.2 and 0.4 ug decreased the number of erections; 0.4 ug also increased the latency to the first glans erection; and 0.8 ug baclofen completely inhibited penile responses in these tests. None of these doses, however, prevented rats from copulating to ejaculation. In contrast to inhibitory effects of baclofen in the lumbosacral cord, intrathecal injection of 0.8 ug baclofen at thoracic segments (T8-T10) did not affect penile erections elicited after an ejaculation. The role of spinal GABAA receptors in sexual reflexes was assessed by intrathecal injection of 0.5, 1, or 2 ug of the GABAA agonist 4,5,6,7-tetrahydroisoxazolo[5,4-c]pyridin-3-ol into the lumbosacral cord. Only with the largest dose of 4,5,6,7-tetrahydroisoxazolo[5,4-c]pyridin-3-ol mild inhibitory effects on penile reflexes were observed. These data indicate that stimulation of GABAB receptors in the lumbosacral spinal cord inhibits erectile mechanisms *ex copula* [58] .

In contrast, Paredes and Agmo [52] injected CGP 35348, a GABAB antagonist, intraperitoneally in rats, completely blocking the inhibitory effect of baclofen on sexual behavior at a dose of 100 mg/kg. The antagonist itself had no effect on these functions. This observation corroborates the GABAB receptor-mediated inhibitory effect of baclofen on sexual behavior.

Denys *et al* [54] investigated 9 men with multiple sclerosis or spinal cord injury, treated with intrathecal baclofen administered by a telemetric pump; average follow-up was 44.4 months. Eight patients reported a decrease of erection rigidity and/or duration while being treated with intrathecal baclofen. The authors concluded that intrathecal baclofen may compromise penile erection and ejaculation, but in a reversible manner.

In 2 cases of idiopathic nocturnal priapism reported by Rourke *et al*, [59] 40 mg baclofen taken at bedtime led to a complete resolution of symptoms while preserving normal erectile function. A dose-response effect was demonstrated and treatment response was durable in both patients at 5- and 12- month follow-up. In the authors' opinion oral baclofen represents an agent for recurrent nocturnal priapism therapy and may also represent the ideal treatment for episodic priapism in patients with sickle cell disease.

This is the first report about the utility of intrathecal baclofen for the successful control of otherwise untreatable priapism in a patient with severe spinal spasticity.

In our opinion a reduction of supraspinal control on the spinal cord may have induced an up-regulation of GABAB receptors, which are involved in penile tumescence. The trauma induced also liberation of penile reflexes with episodes of priapism. Normal full blood count and color duplex ultrasonography of the penis excluded a vascular genesis of priapism.

Hence, evaluation of intrathecal baclofen should be considered in patients suffering from severe and/or frequent priapism when oral baclofen and/or hormonal therapy are ineffective.

Conclusion

Spinal cord injury has a significant impact on the physiological responses of sexual arousal and orgasm, although sexual desire perception is not significantly altered. Since people with SCI remain sexually active, some of the barriers to sexual fulfillment including

neutering perspectives, internal oppression, and loss of physical sensation, should be overcome. Individuals with SCI and their partners may realize a sex life that is less genitally-focused, more creative and mutually rewarding and neurologists should discuss about sexual issues while approaching SCI patients, since sexuality is a fundamental part of any individual's Quality of life. Indeed, it is important to continue counseling and education in this area to prevent health professionals perpetuating the myth that disabled persons are asexual.

References

[1] National Spinal Cord Injury Statistical Center. Spinal cord injury: facts and figures at a glance. *J. Spinal Cord med.* 2005;28:379-380.

[2] Ho CH, Wermser LA, Priebe MM, Chiodo AE, Scelza WM, Kirshblum SC. Spinal Cord injury medicine.1. Epidemilogy and Classification. *Arch. Phys. Med. Rehabil.* Vol 88, Suppl 1, March 2007.

[3] Tator CH, Duncan EG, Edmonds VE, Lapczak LI, Andrews DF. Changes in epidemiology *Surg. Neurol.* 1993;40:207-15

[4] Pagliacci MC, Celani MG, Spizzichino L, Zampolini M, Franceschini M; Gruppo Italiano Studio Epidemiologico Mielolesioni (GISEM) group Hospital care of postacute spinal cord *Am. J. Phys. Med. Rehabil.* 2008;87:619-26.

[5] Citterio A, Franceschini M, Spizzichino L, Reggio A, Rossi B, Stampacchia G. Non traumatic spinal cord injury. An Italian survey. *Arch. Phys. Med. Rehabil.* 2004;85;1483-7.

[6] Harkey III HL, With IV EA, Tibbs RE and Haines DE. A Clinician's View of Spinal Cord Injury. *The Anatomical Record* (part B; New Anat.) 271B:41-48, 2003.

[7] Biering-Sorensen F and Sonksen J. Sexual function in spinal cord lesioned men. *Spinal Cord*. 2001 ;39:455-70.

[8] Bors E, Comarr A. Neurological disturbances of sexual function with special references to 529 patients with spinal cord injury. *Urol. Survey*. 1960; 10:191-222.

[9] Dikaios S. If not the disability, then what? Barriers to reclaiming sexuality following spinal cord injury. *Sex Disabi*.l 2006,24:101-11.

[10] Deforge D, Blackmer J, Garritty C, et al. male erectile dusfunction following spinal cord injury: a systematic review. *Spinal Cord.* 2006;44;465-73.

[11] Ricciardi R, Szabo CM, Poullos AY. Sexuality and Spinal cord injury. *Nursing Clinics of North America*. 2007;42:675-684.

[12] Ramos AS, Samso JV. Specific aspects of erectile dysfunction in spinal cord injury. *Int. J. Impot. Res.* 2004;16(supp 2):S42-5.

[13] Monga M, Bernie J, Rajasekaran M. Male infertility and erectile dysfunction in spinal cord injury. *Arch. Phys. Med. Rehabil.* 1999,80:1331-9.

[14] Sipski ML, Alexander CJ, Rosen R. Sexual arousal and orgasm in woman: effects of spinal cord injury. *Ann. Neurol.* 2001;49(1):51-5.

[15] Ferreiro–valasco ME, Barca-Buyo A, de la Barrera SS, et al. Sexual issues in a smaple of womwn with spinal cord injury. *Spinal cord injury*. 2005;43:51-5.

[16] Smith EM, Bodner DR. Sexual dysfunction after spinal cord injury. *Uro*l. *Clin. Nort. Am.* 1993;20(3):535-42.
[17] Guttmann L (ed). The sexual problem (Chapter 29). In: Spinal cord injuries. Comprehensive management and research, 2nd ed. Oxford, London, Edinburgh, Melbourne: Blackwell Scientific Publication WH, 1976, pp 474-505.
[18] Adams DB, Victor M (eds). Diseases of the bspinal cord. In: Principles of neurology, 4th ed. New York: McGraw Hill, 1989, pp 718-754.
[19] Siosteen A et al. Sexual ability, activity, attitudes and satisfaction as part of adjustment in spinal cord-injured subjects. *Paraplegia*. 1990; 28:265-70.
[20] Beretta G, Zonollo A, Fanciullacci F, Catanzaro F. intracavernous injection of papaverine in paraplegic males. *Acta Neurol. Fertil.* 1986;17:283-284.
[21] Chapelle PA, Durand J, lacert P. Penile erection following complete spinal cord injury in man. Br J Urol 1080; 52:216-219.
[22] Tay HP, Juma S, Joseph AC: psycogenic impotence in spinal cord injury patients. *Arch. Phys. Med. Rehabil.* 1996; 77:391-393.
[23] Beric A, Light J. Anorgasmia in anterior spinal cord syndrome. *J. Neurol. Neurosurg. Psychiatry.* 1993; 56:548-51.
[24] Alexander CJ, Sipsky ML, Findler TW. Sexual activities, desire, and satisfaction in males pre- and post-spinal cord injury. *Arch. Sex. Behav.* 1993; 22:217-28.
[25] Nehra A, Werner MA, Bastuba M, Title C, Oates RD. Vibratory stimulation and rectal probe electroejaculation as therapy for patients with spinal cord injury: semen parameters and pregnancy rates. *J. Urol.* 1996; 155:554-9.
[26] Rees PM, Fowler CJ, Maas CP. Sexual Dysfunction 2: Sexual function in men and women with neurological disorders. *The Lancet* 2007; 369:512-25.
[27] Podnar S, Oblak C, Vodusek DB. Sexual function in men with cauda equina lesions: a clinical and electromyographic study. *J. Neurol. Neurosurg. Psychiatry.* 2002; 73:715-20.
[28] Tay HP, Juma S, Joseph AC. Psychogenic impotence in spinal cord injury patients. *Arch. Phys. Med. Rehabil.* 1996; 77: 391 - 393.
[29] Courtois FJ, Goulet MC, Charvier KF, Leriche A. Posttraumatic erectile potential of spinal cord injuredmen: how physiologic recordings supplement subjective reports. *Arch. Phys. Med. Rehabil.* 1999; 80: 1268 -1272.
[30] Grith ER, Tomoko MA, Timms RJ. Sexual function in spinal cord-injured patients: a review. *Arch. Phys. Med. Rehabil.* 1973; 54: 539-543.
[31] Tsuji I, Nakjima F, Morimoto J, Nounaka Y. The sexual function in patients with spinal cord injury. *Urol. Int.* 1961; 12:270-280.
[32] Sipski ML. Sexual functioning in the spinal cord Injured. *Int. J. Import. Res*. 1998;10 (suppl 2): S1 28-30, (discussion: S 1 38- 40).
[33] Jonson RD. Descending pathway modulationg the spinal circuitry for ejaculation: effects of chronic spinal cord Injury. *Prog. Brain Res.* 2006;152:415-26.
[34] Allard J, Truitt WA, McKenna KE, et al. Spinal cord control of ejaculaton. *World J. Urol.* 2005;23(2):119-26.
[35] Brown DJ, Hill ST, Baker HW. Male fertylity and sexual function after spinal cord Injury. *Prog. Brain Res.* 2006;152:427-39.
[36] Linsenmeyer TA. Sexual fucntion and infertility following spinal cord Injury. *Phys. Med. Rehabil.Clin. N. Am.* 2000;11:141-56.

[37] Linsenmeyer TA, Perkash I. Infertility in men with spinal cord injury. *Arch. Phys. Med. Rehabil.* 1991;72:747-54.

[38] Singh R, Rohilla RK, Siwach R, Singh Dhankar S, Kumar Magu N, Singh Sangwan S.Health-related problems and effect of specific interventions in spinal cord injury. An outcome study in Northen India. *Eur. J. Phys. Rehabil. Med.* 2010;46:47-53.

[39] Elliot SL. Problems of sexual function after spinal cord injury. *Prog. Brain Res.* 2006;152:387-399.

[40] Valtoren K, Karlsson AK, Siosteen A, et al. Satisfaction and sexual life among persons with traumatic spinal cord injury and meningomyelocele. *Disabil. Rehabil.* 2006,28:965-76.

[41] Anderson KD, Borisoff JF, Johnson RD, et al. The impact of spinal cord injury on sexual function: concerns of the general population: *Spinal. Cord.* 2007,45:328-37.

[42] Forsythe E, Horsewell JE.Sexual adjustment and quality of rehabilitation of womwn with a spinal cord injury. *Spinal Cord.* 2006;44:234-41.

[43] Anderson KD, Borisoff JF, Johnson RD, et al. Spinal cord injury influences psychogenic as well as physical components of female sexual ability. *Spinal cord*. 2007;45:349-59.

[44] Kreuter M, Sullivan M, Dahlöf AG, Siösteen A. Partener relationships, functioning, mood and global quality of life in personwith spinal cord injury and traumatic brain injury. *Spinal Cord.* 1998,36: 252-261.

[45] Reitz A, Tobe V, Knapp PA, Schurch B. Impact of spinal cord injury on sexual health and quality of life. *Int. J. Impot. Res.* 2004,16:167-174.

[46] Anderson KD, Borisoff JF, Johnson RD, Stiens SA, Elliot SL. Long term effects of spinal cord injury on sexual function in men: implications of neuoplasticity. *Spinal Cord* 2007; 45:338-348.

[47] Sipski ML, Alexander CJ. Sexual activities, response and satisfaction in women pre and post-spinal injury. *Arch. Phys. Med. Rehabil.* 1993;74:1025-1029.

[48] Ide M, Fugl-meyer AR. Life satisfaction in person with spinal cord injury: a comparative investigation between Sweden and Japan. *Spinal cord.* 2001:39:387-393.

[49] Gianino JM, York MM, Paice JA, Shott S. Quality of life: effect of reduced spasticity fromintrathecal baclofen. *J. Neurosci. Nurs.* 1998; 30: 47–54.

[50] Taricco M, Adone R, Pagliacci C, Telaro E. Pharmacological interventions for spasticity following spinal cord injury. Cochrane Database Syst Rev 2000; (2): CD001131.

[51] Bitran D, Miller SA, McQuade DB, et al. Inhibition of sexual reflexes by lumbosacral injection of a GABA-B agonist in the male rat. *Pharmacol. Biochem. Behav.* 1988;31:657–666.

[52] Paredes RG, Agmo A. The GABA-B antagonist CGP 35348 inhibits the effects of baclofen on sexual behavior and motor coordination. *Brain Res. Bull.* 1995;36:495–497.

[53] Vaidyanathan S, Watt JW, Singh G, et al. Management of recurrent priapism in a cervical spinal cord injury patient with oral baclofen therapy. *Spinal Cord.* 2004;42:134–135.

[54] Yamashita N, Hisasue S, Kato R, et al. Idiopathic stuttering priapism: recovery of detumescence mechanism with temporal use of antiandrogen. Urology. 2004;63:1182–1184.

[55] D'Aleo G, Rifici C, Kofler M, Saltuari L, Bramanti P. Favorable response to intrathecal, but not oral, baclofen of priapism in a patient with spinal cord injury. *Spine.* 2009:3:E127-9.
[56] Montague DK, Jarow J, Broderick GA, et al. American Urological Association guideline on the management of priapism. *J. Urol.* 2003;170:1318–1324.
[57] Bitran D, Miller SA, McQuade DB, et al. Inhibition of sexual reflexes by lumbosacral injection of a GABA-B agonist in the male rat. *Pharmacol. Biochem. Behav.* 1988;31:657–666.
[58] Denys P, Mane M, Azouvi P, et al. Side effects of chronic intrathecal baclofen on erection and ejaculation in patients with spinal cord lesions. *Arch. Phys. Med. Rehabil.* 1998;79:494–496.
[59] Rourke KF, Fischler AH, Jordan GH. Treatment of recurrent idiopathic priapism with oral baclofen. *J. Urol.* 2002;168:2552–2553.

In: Male Sexual Dysfunctions in Neurological Diseases… ISBN 978-1-61761-855-0
Editor: Calabrò Rocco Salvatore

Chapter 9

Sexuality in Other Neuropsychiatric Disorders

Giuseppe Gervasi, Domenico Italiano, Carmela Rifici, Giuseppina Digangi, Placido Bramanti, and Rocco Salvatore Calabrò

Abstract

Neuropsychiatric disorders frequently alter sexual response by changing the processing of sexual stimuli to preclude arousal or by decreasing or increasing desire or by curtailing genital engorgement. Patients with a neurological, and/or a psychiatric disease can challenge the ability to communicate, embrace, stimulate, engage in intercourse, and maintain urinary and bowel continence during sexual activity. Beside the major neurological disorders, such as multiple sclerosis, stroke and epilepsy, other important neuropsychiatric illness can cause or can be associated to sexual dysfunction. Herein we report on the most common sexual disorders secondary to brain injury, polyneuropathy, myopathy and major psychiatric illness, such as schizophrenia. Sexual headache, sleep-related and iatrogenic sexual disorders are also discussed.

9.1. Brain Injury

Sexual impairment is a commonly described consequence of traumatic brain injury (TBI). Indeed, many authors believe that sexual dysfunction is "more often the rule than the exception". A brain trauma could involve all those brain regions activated during a normal sexual response. Nevertheless, sexual impairment in injured people seems to be related both to a direct effect of trauma on sexual pathway and to a situational change in the patient's mood, the latter contributing to higher rates of sexual dysfunction after brain trauma (about 36-54%) [1]. Sexual dysfunctions after TBI are more reported in men than in women, and mostly in severe rather than minor trauma [2].

Some investigators reported that sexual disorders do not correlate with cognitive impairment, length of post-traumatic amnesia or physical neurological disability caused by brain injury. Independent determinants of sexual outcome include a high sickness-impact profile, low-self-esteem, anxiety and depression, which are considered the most sensitive negative predictor.

Physiopathology and type of sexual disorders of post TBI patients are closely dependent on the damaged brain area, although poor attention has been paid on understanding the specific nature or the impact of sexual dysfunction in these individuals. The most reported sexual dysfunctions in men after TBI are erectile dysfunction (ED) and disorders of desire, mainly when anterior brain regions are damaged.

ED is considered to be due either to post TBI depression or to damage of the hypothalamic-pituitary axis. Indeed, although many authors reported that head injured males experience ED when associated to depression, it has recently been found how erectile problems are often accompanied by signs and symptoms of cerebral damage and impaired libido.

Changes in sexual desire and behavior are by far the most common sexual problem after a brain injury. Since anterior brain regions are associated with emotional and behavioral impairment, prefrontal and lobar lesions might more frequently generate hyposexuality rather than hypersexuality. The latter is often reported as an intensified sexual experience after brain injury, an inappropriate sexual attention towards others, or a kind of sexual exhibitionism leading to sexually deviant criminal activities (i.e. rape or pedophilia) [3-7]. Many authors have reported that "the sexual activity of injured subjects is often a one-side act, done without regard for the partner". Hypersexuality and alteration of sexual preference provide important clues for understanding the anatomy and physiology of human sexual behavior. Lesions in structures such as the amygdala, the hypothalamus, the temporal and frontal lobes have been described in association to these symptoms. In particular, lesions in the frontal lobe have been referred as an anatomical site producing true hypersexuality while the other structures are more related to changes of sexual preference [8, 9].

Interestingly paraphilia has been described as occurring after brain damage, mostly of the frontal lobes and diencephalic structures. As Paraphilia rarely occurs after the age of 30, an acquired paraphilia onset in elderly people is often associated with focal brain injury [5, 7]. Many authors have tried to investigate the role of TBI in sex offenders with inconclusive results related to complexity of this study. Lagevin has pointed out that 22.5% of sex offenders presented a previous TBI, sometimes associated to lifestyle factors such as drug abuse or alcohol consumption. In some case brain injury is a direct result of an aberrant lifestyle. Moreover, sex offenders with a TBI history might be distinguishable from those without it. Indeed, they showed a tendency to act out more with adults than with children and a polymorphous fashion of their sexual behavior [10].

On the contrary, hyposexuality is more related to the psychological aspect of sexuality. People with TBI reported more frequently difficulties in sexual activity and relationship than in erectile function. Many patients report difficulties in positioning, body movement and decreased sensation, negatively impacting on their sexual activities and interest. These findings suggest a relationship among sexual satisfaction, level of dependence and degree of handicap leading to a negative body image and low self-esteem in sexual activities. Indeed, psychological factors could be the best predictor of hyposexuality in men after TBI.

Moreover, severity of TBI has been suggested as an important predictor of sexual disorders. However, since the global amount of brain tissue destroyed seems to be related to the awareness level, sexual dysfunctions are more often reported in patients with milder than severe injuries. Inconsistent results were found across studies on the effect of time post TBI. Some authors have found a close relationship between length of time after TBI and severity of sexual impairment, with shorter duration of time associated with better sexual function and satisfaction. Nevertheless, recent studies have pointed out how sexual difficulties could develop at any time post TBI as well as at any age [11].

Lesions of the frontal and temporal lobe seem to lead more frequently to sexual problems than lesions of the posterior part of the brain. Disorder of ejaculation has also been reported in patients after a brain trauma with delayed ejaculation as the most frequent symptom (from 17% to 36%) and premature ejaculation with an incidence of 9% [12, 13]. Some authors have described cases of sexual hyperarousal and increased skin sensitivity of penis following minor TBI in healthy persons, suggesting a secondary rather than primary (neurogenic) origin of premature ejaculation [2, 11, 14, 15].

Hypotalamo-pituitary Trauma

Injury of pituitary gland is a frequent complication of head trauma and it is associated with high mortality rate during the acute phase. Serious and life-threatening adrenal crisis due to adrenocorticotropic deficiencies following TBI is widely highlighted in many clinical studies. Occurrence of a fatal panhypopituitarism after TBI is associated with severity of head trauma. Diffuse axonal injury, basal skull fracture and increased intracerebral pressure are the most frequent physiopathological mechanisms determining panhypopituitarism. Recovery between 6 and 12 months is almost always the rule, when hypopituitarism is quickly diagnosed and treated.

The prevalence of endocrine dysfunction after TBI, due to anterior pituitary lesions, ranges from 15% to 68%. Both anterior and posterior parts of the gland could be damaged. Hemorrhage, necrosis and fibrosis in the context of pituitary gland are common complications of TBI. Moreover, they are often associated with hypothalamopituitary impairment of the chronic TBI phase [16].

Lesion of the anterior part of pituitary gland is associated with altered sexual desire related to Luteinizing Hormone (LH), Follicle-Stimulating Hormone (FSH), Prolactin (PRL) and Growth Hormone (GH) alterations. LH and FSH deficiency is associated with central hypogonadism, especially when trauma occurs during childhood. Central hypogonadism is also reported from 9 to 23% of men with low gonadotropin response or low testosterone levels after TBI, while reduced GH levels could influence sexuality through reduction of energy levels and general wellbeing.

Hyperprolactinemia is more associated with orgasm, libido and arousal disturbances in women rather than in men. The high levels of PRL are thought to be a consequence of antidepressants and antipsychotic treatment rather than a direct effect of trauma.

Studies on the association of sexual dysfunction and anterior pituitary hormone impairment after TBI need further investigations [17].

Lesions of the posterior part can cause a central diabetes insipidus due to depressed antidiuretic hormone blood level. Sexual dysfunctions following posterior pituitary trauma

often occur with altered sexual arousal due to low oxytocin blood level, especially in women. Nevertheless, oxytocin has also inhibitory properties concerning postcoital satiety and male refractory period [18].

Deficiency in neuropeptidergic molecules as hypothalamic Orexin-A (i.e. Hypocretin-1) is sometimes associated with TBI. Orexins are involved in regulation of sleep-wake cycle and low levels are often evidenced in patients in the subacute phase of moderate to severe TBI. In these patients, levels of hypocretin-1 in the cerebrospinal fluid are comparable to those of narcoleptic patients. Reduced cerebrospinal fluid levels of Orexins are associated with hypersomnolence which may interfere with the normal sexual intercourse, behavior and arousal of posttraumatic patients [2, 19].

Klùver-Bucy Syndrome

Klùver-Bucy Syndrome (KBS) is one of the most common temporo-limbic syndromes caused by a bilateral damage of anterior temporal lobes. KBS is quite frequent in post TBI patients due to the injury of temporal and orbitofrontal areas with the bone of middle and anterior cranial fossae.

In 1939 Klùver and Bucy bilaterally removed the anterior temporal lobes in primates and noted six different neuropsychiatric symptoms, i.e. "Psychic blindness", hypersexuality, altered emotional behavior, hyperorality, "hypermetamorphosis" and memory deficit, related to limbic cortex and amygdala involvement. They termed psychic blindness as the inability of animals to recognize emotional significance of the object, while they used hypermetamorphosis to indicate the tendency to react to every visual stimulus especially with the mouth. Indeed, their animals became tame with an excessive and sometimes life-threatening oral exploration of the environment.

In humans, KBS is rare and described as typical in the post-traumatic remission phase and associated with favorable prognosis in the outcome of traumatic disturbances of consciousness in survivors of head trauma [20]. Human KBS is a more complex behavioral syndrome. Some authors attribute this complexity to the evolutionary advances of the human brain. Therefore, patients with KBS didn't show the full-blown syndrome but often other accompanying symptoms such as aphasia, amnesia, echopraxia, dementia and seizures. The presence of at least 3 of the 6 aforementioned main symptoms is mandatory for the diagnosis. Among humans, altered emotional behavior and hyperorality are the most common features, while hypersexuality is less common.

Alterations in emotional behavior in humans include apathy, lethargy and emotional unresponsiveness, whereas KBS patients with aggressive and hypomaniac mood associated with hyperorality and hyperphagia have been reported.

Hypersexuality presented itself with a wide clinical spectrum varying form an inappropriate or obscene language in specific contexts to a dirty behavior acting with whatever person. The most reported symptoms are changes in sexual orientation, compulsive masturbation, inappropriate sexual remarks and gestures without care of situation.

Frequent causes of KBS are infectious diseases such as herpes virus encephalitis, hypoxia, hepatic and metabolic impairment. KBS is also observed in cases of pontine mielinolysis related to rapid correction of hyponatremia, or following temporal status epilepticus when associated with bilateral mesial temporal sclerosis. The latter could explain

the easy response to carbamazepine treatment in these subjects. KBS episodes are often reported in severe TBI patients during recovery of awareness, especially when MRI shows a mesial and/or basal temporal lobe involvement [21-23].

Specific sides of the disease are still under debate. Although many authors have highlighted the role of the two amygdalae, recently someone has shown how the disruption of limbic circuitry associated with mediodorsal thalamic relay could develop KBS. The complex pathways connecting the dorsomedial thalami with prefrontal or limbic areas are essential for memory and regulation of impulses and emotions. This cerebral circuitry involvement could explain the symptoms variability of KBS in humans [24-26].

References

[1] Sandel ME, Williams KS, Dellapietra L, Derogatis LR. Sexual functioning following traumatic brain injury. Brain Inj. 1996 Oct;10(10):719-28.

[2] Rees PM, Fowler CJ, Maas CP. Sexual function in men and women with neurological disorders. Lancet. 2007 Feb 10;369(9560):512-25.

[3] Miller BL, Cummings JL, McIntyre H, Ebers G, Grode M. Hypersexuality or altered sexual preference following brain injury. J Neurol Neurosurg Psychiatry. 1986 Aug;49(8):867-73.

[4] Simpson G, Blaszczynski A, Hodgkinson A. Sex offending as a psychosocial sequela of traumatic brain injury. J Head Trauma Rehabil. 1999 Dec;14(6):567-80.

[5] Simpson G, Tate R, Ferry K, Hodgkinson A, Blaszczynski A. Social, neuroradiologic, medical, and neuropsychologic correlates of sexually aberrant behavior after traumatic brain injury: A controlled study. J Head Trauma Rehabil. 2001 Dec;16(6):556-72.

[6] Mutarelli EG, Omuro AM, Adoni T. Hypersexuality following bilateral thalamic infarction: Case report. Arq Neuropsiquiatr. 2006 Mar;64(1):146-8.

[7] Bianchi-Demicheli F, Rollini C, Lovblad K, Ortigue S. "Sleeping beauty paraphilia": Deviant desire in the context of bodily self-image disturbance in a patient with a fronto-parietal traumatic brain injury. Med Sci Monit. 2010 Feb;16(2):CS15-7.

[8] Graff-Radford NR, Damasio H, Yamada T, Eslinger PJ, Damasio AR. Nonhaemorrhagic thalamic infarction. clinical, neuropsychological and electrophysiological findings in four anatomical groups defined by computerized tomography. Brain. 1985 Jun;108 (Pt 2)(Pt 2):485-516.

[9] Eslinger PJ, Warner GC, Grattan LM, Easton JD. "Frontal lobe" utilization behavior associated with paramedian thalamic infarction. Neurology. 1991 Mar;41(3):450-2.

[10] Langevin R. Sexual offenses and traumatic brain injury. Brain Cogn. 2006 Mar;60(2):206-7.

[11] Hibbard MR, Gordon WA, Flanagan S, Haddad L, Labinsky E. Sexual dysfunction after traumatic brain injury. NeuroRehabilitation. 2000;15(2):107-20.

[12] Meyer JE. Sexual disorders in brain injured. Arch Psychiatr Nervenkr Z Gesamte Neurol Psychiatr. 1955;193(5):449-69.

[13] Kreutzer JS, Zasler ND. Psychosexual consequences of traumatic brain injury: Methodology and preliminary findings. Brain Inj. 1989 Apr-Jun;3(2):177-86.

[14] Simpson G, McCann B, Lowy M. Treatment of premature ejaculation after traumatic brain injury. Brain Inj. 2003 Aug;17(8):723-9.
[15] Zasler ND. Subject review on head injury and sexual dysfunction. Brain Inj. 1997 May;11(5):389-90.
[16] Schneider HJ, Kreitschmann-Andermahr I, Ghigo E, Stalla GK, Agha A. Hypothalamopituitary dysfunction following traumatic brain injury and aneurysmal subarachnoid hemorrhage: A systematic review. JAMA. 2007 Sep 26;298(12):1429-38.
[17] Lieberman SA, Oberoi AL, Gilkison CR, Masel BE, Urban RJ. Prevalence of neuroendocrine dysfunction in patients recovering from traumatic brain injury. J Clin Endocrinol Metab. 2001 Jun;86(6):2752-6.
[18] Bancroft J. The endocrinology of sexual arousal. J Endocrinol. 2005 Sep;186(3):411-27.
[19] Baumann CR, Stocker R, Imhof HG, Trentz O, Hersberger M, Mignot E, et al. Hypocretin-1 (orexin A) deficiency in acute traumatic brain injury. Neurology. 2005 Jul 12;65(1):147-9.
[20] Formisano R, Saltuari L, Gerstenbrand F. Presence of kluver-bucy syndrome as a positive prognostic feature for the remission of traumatic prolonged disturbances of consciousness. Acta Neurol Scand. 1995 Jan;91(1):54-7.
[21] Naito K, Hashimoto T, Ikeda S. Kluver-bucy syndrome following status epilepticus associated with hepatic encephalopathy. Epilepsy Behav. 2008 Feb;12(2):337-9.
[22] Tuleja E, Chermann JF, Sereni C, Hart G, Sereni D. Kluver bucy syndrome, unusual consequence of excessively rapid correction of severe hyponatremia. Presse Med. 2008 Jun;37(6 Pt 1):975-7.
[23] Jha S, Patel R. Kluver-bucy syndrome -- an experience with six cases. Neurol India. 2004 Sep;52(3):369-71.
[24] Hayman LA, Rexer JL, Pavol MA, Strite D, Meyers CA. Kluver-bucy syndrome after bilateral selective damage of amygdala and its cortical connections. J Neuropsychiatry Clin Neurosci. 1998 Summer;10(3):354-8.
[25] Carroll BT, Goforth HW, Carroll LA. Anatomic basis of kluver-bucy syndrome. J Neuropsychiatry Clin Neurosci. 1999 Winter;11(1):116.
[26] Trimble MR, Mendez MF, Cummings JL. Neuropsychiatric symptoms from the temporolimbic lobes. J Neuropsychiatry Clin Neurosci. 1997 Summer;9(3):429-38.

9.2. Sexual Headache

The second edition of the International Headache Society (IHS) classification defines “headache associated with sexual activity” (HSA) as bilateral headache precipitated by sexual excitement (masturbation or coitus), which occurs in the absence of any intracranial disorder and which can be prevented or eased by ceasing sexual activity before orgasm [1].

The IHS classification differentiates two types of HSAs. Type 1 is a dull ache in the head and neck associated with the awareness of neck and/or jaw muscle contraction which increases with sexual excitement. It is also called preorgasmic headache. Type 2, so-called orgasmic headache, is a sudden severe (‘explosive’) headache which occurs in orgasm [2].

A third type of sex-related headache consisting in a holocephalic, late coital, long lasting headache, has been classified as a secondary headache disorder, since its clinical features (most severe in an upright position and improving with recumbency) are consistent with low CSF pressure headache [3].

HSAs are rare and only a few studies have investigated the epidemiological aspects. The exact prevalence of HSA is unknown. Until 1986, 110 cases of HSA had been reported in the available literature [2]. In the only population-based epidemiological study, the lifetime prevalence was about 1% [4]. It is likely that the prevalence of this headache is underestimated, since patients often feel embarrassed to report intimate details about their sexual activities. A 3-4:1 male to female ratio more is reported for HSA. The mean age at onset is between 30 and 40 years old, with a first peak between the ages of 20 and 30 and the second between 35 and 44 [2]. About 22% of patients experiencing HSA have preorgasmic, while the remaining 78% have the orgasmic variant. The mean duration of severe pain is similar for both types of HSA (30 minutes), but the mean duration of milder pain is more prolonged with type 2 (4 hours vs. 1 hour). The time of onset, however, is by definition different for the 2 types. In type 2 it occurs simultaneously with orgasm or less than 5 seconds before, while in type 1 it has a mean time of onset of 150 seconds preceding orgasm [3].

Migraine is comorbid in 30% of type 2 patients as opposed to 9% of those with type 1. Comorbid primary exertional headaches are also seen in 35% of type 2 cases while only seen in 9% of type 1 patient [5, 6].

The usual setting for both types is sexual intercourse with the patient's usual partner; however, 1/3 reports it with masturbation as well. A certain percentage of patients report that they can terminate the headache by stopping sexual activity; 51% report that they can lessen the pain intensity by taking a more passive role [2]. In most cases, these headaches seem to occur in bouts that recur over a period of weeks to months before resolving.

The exact pathophysiology of HSA is unknown. The pathophysiologic mechanisms proposed for sexual headaches are largely speculative. It was supposed that HSA exhibits as main mechanism a trigeminal vascular effect, but a definite muscular component is also present. Muscular contraction plays a major role especially in milder headaches that become more intense as the sexual excitement increases (type 1 HSA) [3,7,8]. Lance proposed that Type 1 sexual headache arises from excessive contraction of neck and jaw muscles during sexual activity and might be avoided by conscious relaxation of these muscles during intercourse [9].

Explosive (Type 2) headaches are attributed to rapid increases in blood pressure and heart rate that occur during orgasm. Indeed during orgasm, blood pressure may increase by 40-100 mmHg systolic and 20-50 mmHg diastolic, and this physiologic change has been suggested to play a role in the genesis of HSA [7-9]. Studies indicate that patients who experience type 2 headaches may have impaired cerebrovascular autoregulation. The cerebral vessels of these patients may dilate unpredictably in response to low pH as compared to normal healthy control [10, 11]. Some authors suggest that there is a possible link between type 2 headaches and migraines, and have postulated a release of catecholamines, neurokinins and serotonin during HAS [5, 6]. High blood pressure, pre-existing migraine and psychological factors are predisposing factors. HSA is more common in middle-aged hypertensive or obese males. The partial response of orgasmic headache to triptan therapy indirectly supports a pathophysiological similarity to migraine.

Since the third type of HSA resembles the clinical picture of a low pressure headache, it has been postulated to be pathophysiologically related to an acquired CSF leak. In particular it may arise from a tear or widening of a tear in the arachnoid mater during sexual intercourse [3].

Prognosis of HSA is good and should be explained to the patient. There is no treatment in the acute phase. As a preventive step, sexual activity could be stopped during the bout of headache, and a passive role can be beneficial. However, HSAs are not always benign. Presentation of headache can mimic conditions such as subarachnoid haemorrhage, vascular thrombosis, hemispherical infarction, reversible sensory disturbances and homonymous hemianopia. Thus, they can be confused with "thunderclap" headaches that occur during coitus and signal a sudden intracranial event, such as subarachnoid haemorrhage.

With the first episode it is mandatory to exclude potential life-threatening and disabling causes. There are estimates that subarachnoid hemorrhage occurs in 4-12% of cases of all cases of headache occurring during sexual activity (3). An accurate anamnesis can help to differentiate the benign coital headache from more malignant causes such as subarachnoid haemorrhage: isolated coital cephalalgia is usually repetitive, unpredictable and episodic, while severe headaches lasting for more than 24 hours or associated with a loss of consciousness are unlikely to be HSA.

However, a prompt and thorough neurological examination is imperative, as well as evaluation for vascular abnormality or subarachnoid hemorrhage with brain CT and lumbar puncture (if within hours of the onset) or brain MRI (if days or weeks have elapsed). This is especially important when the headaches are explosive (type 2). In fact, to meet the IHS criteria for the diagnosis of headache associated with sexual activity, structural causes must be excluded [1].

Orgasmic headache can be frightening, distressing and disabling. After serious underlying pathology has been excluded by the appropriate investigations, the most important aspect of treatment is to reassure the patient and partner about this usually benign, self-limited disorder. In the majority of patients the headache disappears without any specific treatment. Nevertheless, acute or prophylactic treatment can be necessary in patients with severe acute pain or with repeated attacks. Follow-up studies investigating HSA prognosis showed recurrence rates from 33% to 50% after 6 years [12]. The presence of concomitant primary headache syndromes (migraine or tension-type headache) was hypothesized to be a risk factor for recurrence of HSA. Concomitant exertional headache and an early onset of the disease seem to be associated with an episodic course of HSA, whereas a later onset of the disease seems to be associated with a chronic course. HSA attacks are usually short lasting without need for acute medical treatment but the duration of pain varies widely. About 15% of patients suffer from severe pain for 4 h up to 24 h, necessitating effective acute treatment. Indomethacin has also been suggested for acute treatment of HSA, showing good results in 90% of cases [12]. Triptans seem to be an alternative option for those patients not tolerating indomethacin. For triptans with low absorption rates (such as naratriptan), earlier administration 60 min before sexual activity may be favourable [13]. For those patients with longer lasting bouts or with a chronic course of the disease, prophylactic treatment can be indicated. β-blockers (propranolol or metoprolol) can be recommended for prophylaxis of HSA, with success rates of approximately 80% [12].

References

[1] Headache Classification. Committee of the International Headache Society. The International Classification of Headache Disorders, 2nd edn. *Cephalalgia.* 2004;24:9-160.

[2] Frese A, Eikermann A, Frese K, Schwaag S, Husstedt IW, Evers S. Headache associated with sexual activity: demography, clinical features, and comorbidity. *Neurology*. 2003;61:796-800.

[3] Turner IM, Harding TM. Headache and sexual activity: a review. Headache. 2008;48:1254-6.

[4] Rasmussen BK, Olesen J. Symptomatic and nonsymptomatic headaches in a general population. *Neurology* 1992; 42:1225-31.

[5] Silbert PL, Edis RH, Stewart-Wynne EG, et al. Benign vascular sexual headache and exertional headache: interrelationships and long term prognosis. *J Neurol Neurosurg Psychiatry* 1991;54:417–21.

[6] Biehl K, Evers S, Frese A. Comorbidity of migraine and headache associated with sexual activity. *Cephalalgia* 2007;27:1271–3.

[7] Goadsby PJ, Ramadan NM, et al, editors. The headaches. 3rd edition. Philadelphia: Lippincott Williams and Wilkins; 2006. p. 841–5

[8] Pascual J. Other Primary Headaches Neurol Clin 2009;27:557–571

[9] Lance JW. Headaches related to sexual activity. *J Neurol Neurosurg Psychiatry* 1976;39:1226–30.

[10] Heckmann JG, Hilz MJ, Muck-Weymann M, et al. Benign exertional headache/benign sexual headache:A disorder of myogenic cerebrovascular autoregulation*? Headache*. 1997;37:597-598.

[11] Evers S, Schmidt O, Frese A, et al. The cerebral hemodynamics of headache associated with sexual activity. *Pain.* 2003;102:73-78.

[12] Frese A, Rahmann A, Gregor N, Biehl K, Husstedt IW, Evers S. Headache associated with sexual activity: prognosis and treatment options. *Cephalalgia*. 2007;27:1265-70.

[13] Frese A, Gantenbein A, Marziniak M, Husstedt IW, Goadsby PJ, Evers S. Triptans in orgasmic headache. *Cephalalgia*, 2006;26:1458–1461

9.3. Sleep Disorders

A linkage between sleep disorder and sexual dysfunction has been studied worldwide. An underlined sleep disorder in patients suffering from erectile dysfunction (ED) could cause a failure of response to pharmacological treatment. Then, evaluation of sleep quality in these patients has to be promoted as an alternative approach to improve their outcome.

In 2002, Seftel et al. screened all the patients which reported symptoms of ED. Using a home-made questionnaire, they found a prevalence of OSAS symptoms in 26.8% patients with ED, followed by a 13.6% of insomnia, and 2% of RLS and narcolepsy.

To our knowledge, in the last decades several studies have found a predominantly reversible association between ED and Obstructive Sleep Apnea Syndrome (OSAS). Nevertheless, all the sexual dysfunctions could worsen with the presence of sleep disorder

and many sleep disorders could lead to a reversible sexual dysfunction. An accurate assessment and management of sleep disruption can restore the normal sexual function [1,2].

Herein we report a systematic analysis of the most common sleep disturbances presenting with sexual dysfunction.

Severe Chronic Insomnia. A chronic alteration of a normal sleep pattern can determine an altered control of sexual function leading to disorders of desire and finally to ED.

Hyposexuality is the most common sexual dysfunction in subjects with insomnia. Pathophysiology has not been well elucidated. The most reliable hypothesis is a disruption in testosterone secretion in men suffering from sleep disorders. In 1998, Luboshitzky evidencied a nocturnal rise of testosterone in the young shortly after falling asleep that peaked at the first REM episode and lasted at the same level until awakening. This hormonal rise seems to be correlated to the REM latency and influenced by age. Indeed, in the elderly the reduced sleep efficiency and the delayed REM latency could cause a reduction in testosterone levels. At the same time, insomnia can cause a disruption in testosterone rhythm leading to sexual dysfunction such as loss of desire and ED.

Nevertheless, several studies have pointed out the presence of an increased sexual desire in patients suffering from insomnia since the juvenile age. Although there is an evidence of physically exhaustion in these patients, someone can experience during daytime a feeling of mind body speed up and an excessive libido and genital hyperarousal. These patients sometimes reported strong sexual sensations in the genitalia and general sexual heightening without erotic thoughts or altered consciousness that would only partly and briefly be relieved having frequently sex also with different partners. A successful control of insomnia with drugs could control this excessive libido and genital hyperarousal, showing a direct role of the disruption of the sleep in the genesis of this specific sexual dysfunction. Pathophysiology of the hypersexuality in these persons is not even well understood [3].

A video-PSG is mandatory for the diagnosis in order to discover low sleep efficiency and an altered sleep pattern with reduced REM sleep, delayed REM latency and increasing percentage of stage 1 and stage 2. The Nocturnal Penile Tumescence REM sleep Monitoring (NPTRM) with an ambulatory tool could show a high level of false positive results for organic ED, due to the altered REM phases.

OSAS. The most studied sleep disorders associated with sexual dysfunction is by far OSAS. A direct role for sleep apnea in producing ED is suggested by those studies indicating that treatment for sleep apnea with CPAP restores erectile function. To date, several mechanisms have been proposed to understand the pathophysiology of OSAS-related sexual dysfunction. The most important are:

- Dysfunction of pituitary-gonadal axis, due to sleep fragmentation and deprivation causing a significant disruption of the pulsatile testosterone rhythm.
- Increasing sympathetic activity, showed by an increasing plasma level of norepinephrine, especially at night in any sleep disorders, which might be in opposition to the normal physiological mechanisms allowing normal erectile function.
- Peripheral nerve dysfunction, noted from the altered response of the bulbo-cavernous reflex in patient with OSAS suffering ED; the degree of this alteration is related to OSAS severity and nocturnal hypoxia level

- Oxidative stress, due to a high production of reactive oxygen species in OSAS patients (in particular superoxide, hydrogen peroxide and peroxynitrite) that increase the incidence of apoptosis in endothelial cells, leading to denudation of endothelium with a further decrease in NO concentration; these mechanisms collectively inhibit NO-mediated cavernous tissue relaxation.
- Increased production of endothelin, a vasoconstrictor related to the level of hypoxemia during the night that might oppose penile tumescence.

Furthermore, OSAS is often associated to hypertension an diabetics, which are well known risk factors for ED. The presence of these risk factors could sometimes explain the failure of CPAP treatment in improving OSAS-related ED [1].

Video-PSG is the gold standard tool for the diagnosis of OSAS, but a cardio-respiratory screening for sleep apnea with a home-monitoring device is also used to detect the presence of a sleep apnea index (AHI) > 5, that is mandatory for the diagnosis of OSAS. Sexual dysfunction, especially ED, is a common complication of moderate to severe OSAS (AHI > 15).

Narcolepsy. Narcolepsy is a sleep disorder of unknown origin and characterized by four symptoms such as excessive daytime sleepiness, cataplexy, sleep onset (hypnagogic) or sleep offset (hypnopompic) hallucination, sleep paralysis. Diagnosis is made with clinical relevant symptoms and confirmed by video-PSG showing a reduced latency to sleep and REM phase, and an increasing percentage of stage 1 and REM. A subsequently Multiple Sleep Latency Test (MSLT) must detect a mean sleep latency ≤8 minutes and the presence of two or more Sleep Onset REM Periods (SOREMPs). Sexual dysfunctions in narcoleptic patients are not so common.

The most frequent sexual dysfunctions in narcoleptic patients are altered sexual desire and ED. The latter is mainly reported as a side effect of therapy like Modafinil, used for excessive daytime sleepiness, and Selective Serotonine Re-uptake Inhibitors (SSRI) or Tricyclic antidepressant, used for cataplexy.

Altered sexual behaviors are differently reported in narcoleptic patients with cataplexy rather than those without cataplexy. Patients presenting with cataplexy usually experience hyposexuality generally linked with avoidance of intensive feeling provoking cataleptic attack. Otherwise, many clinicians often reported hypersexuality in their narcoleptic patients without cataplexy mostly related to their particular personality. As well as in Kleine-Levine Syndrome, disinhibition in young narcoleptic patients is widely reported. Furthermore, some authors recently found a linkage between narcolepsy, dissociation state and schizotypal personality sharing a common brain domain [4,5].

Restless Legs Syndrome (RLS). RLS is a clinical syndrome characterized by the presence of an irresistible urge to move the legs to avoid a deep sensation in the lower limbs occurring when the subject lies down, especially in the evening in the transition from wake to sleep.

Some reports have pointed out the presence of rhythmic, pelvic, intermittent and stereotyped coital-like movement in patients suffering of RLS during wake-sleep transition. These movements are not accompanied by sexual sensation. They seem to be linked to the classic periodic limb movement of RLS because they are responsive to dopamine agonist treatment such as pramipexole or ropinirole. Some authors have also reported cases of men with compulsive masturbation practice used to alleviate the bothersome sensation of RLS. In these cases orgasm is associated with dopamine and opioid release and mediates the

therapeutic effect on RLS symptoms. Moreover, a hyposexuality in these patients, mainly due to the altered dopaminergic pathways of this disease, has been also demonstrated. Sexual dysfunctions in RLS patients are directly related to the severity of symptoms. Thus, patients with moderate-to-severe RLS often complain of sexual dysfunction. Treatment with dopaminergic agonist could reduce the severity of sexual dysfunctions thanks to a direct action upon the dopaminergic pathways and/or the consequent effect on RLS symptoms. Nevertheless, hypersexuality in patients suffering of RLS is also reported as a side effect of dopaminergic treatment [6].

Kleine-Levine Syndrome (KLS)

KLS is a rare disease characterized by recurrent episodes of hypersomnia and a wide range of cognitive and/or psychiatric disturbances such as compulsive behavior and mood disorders.

KLS is the first cause of recurrent hypersomnia usually affecting adolescent males. Patients are always tired and drowsy during the sleep attack and become irritable or aggressive when awakened or prevented from sleep. Between two different sleep episodes, patients present with attention, memory and confusion defects, derealization or hallucination, depressive mood or sometimes hypomaniac episodes, compulsive behavior and sexual disturbances. Secondary KLS mainly due to neurological disease involving thalamus and brain fronto-temporal areas (i.e. bilateral hypothalamic or thalamic infarct, multiple sclerosis, hydrocephalus, severe infectious or autoimmune encephalitis, brain trauma, paraneoplasia) has been reported, but a primary form of the disease is the most frequent clinical presentation. The pathophysiology of primary KLS is still poorly understood with possible environmental factors acting on a genetic predisposition as the most trustworthy hypothesis. Among environmental factors, KLS episodes could be triggered by severe encephalitis (especially viral infection), a mild to moderate head trauma, or alcohol consumption. Common pathophysiological mechanism is autoimmune encephalitis restricted to the hypothalamus and adjacent area. Indeed, an increasing permeability of blood-brain barrier facilitating the passage of circulating pathogenic agent or immunoglobulin to the brain is thought to be the most plausible pathogenic mechanism.

Sexual disorders are common in KLS patients. Hypersexuality is the most common symptoms presenting in more than half of the patients with a higher prevalence in men than in women. However, hyposexuality is also reported in a lower percentage of episodes (about 20%). Hypersexuality shares the same psychopathology of compulsive behavior in these patients. The intensity of these abnormal behaviors may vary. Some behaviors could be considered as mildly inappropriate when acted in a given context of education or culture (i.e. use of obscene words in front of parents or doctors). On the other hand, sexual disinhibition occurs sometimes simultaneously with other repetitive or stereotypical compulsions (i.e. setting fire), associated to a disturbed state of consciousness that is struggle to describe, and always during an attack of hypersomnia. The presence of sexual dysfunction is often associated with a worsening in the length of the disease.

Clinical examination is unremarkable in all cases of primary KLS. Standard EEG could sometimes detect the presence of slowed activity (delta or theta) in both fronto-temporal areas but without relevant clinical significance. Brain MRI is negative, but functional neuroimaging

may detect a reduced cerebral blood flow in the temporal or fronto-temporal areas in some patients. Diagnosis is almost based on the clinical signs. Medical tests are aimed at eliminating other neurological causes of secondary KLS (mainly infections). A video-PSG could demonstrate the presence of a high length in mean Total Sleep Time during both nocturnal and 24-h recording, with an increased percentage in all sleep stages. MSLT confirm the hypersomnia state with a low account of mean sleep latency and sometimes with a narcolepsy-like pattern (two or more SOREMPs) [7].

Parasomnias and Forensic Considerations

The link between sleep and sex is very intricate. Despite the presence of sexual dysfunctions related to altered sleep-wake cycle, many patients could experience abnormal sexual behaviors during parasomnia. In the International Classification of Sleep Disorders (ICSD-2v), Parasomnia groups all sleep disorders characterized by the presence of undesirable physical phenomena that disrupt the normal sleep. The pathophysiology of this disorder is recently explained with the hypothesis of a dissociative state. According to this theory, every subject exists in one of three different states of being including awake, NREM sleep and REM sleep. Each state is characterized by specific features and commonly they cycle during daytime. A dissociative state is characterized by the association of the characteristics of at least two different states of being in the same subject at the same time. REM Behavior Disorder (RBD) and Narcolepsy are two examples of sleep disorders with a dissociative state. Many patients suffering from RBD could report sexual content of their dream associated with a frankly sexual acts during sleep. Likewise hypnagogic or hypnopompic hallucination in narcoleptic patients could incorporate sexual content.

The so-called *sexsomnia*, characterized only by the recurrent presence of sexual behaviors during sleep, is the most famous parasomnia with only sleep-related sexual activities. Sleepsex behavior is rather used to define the presence of a sexualized act during a parasomnia episode. The most common sleepsex behaviors are masturbation, sexual vocalization, moaning and fondling rather than sexual intercourse itself. Sleepsex behavior could be found in patients presenting with sleep related seizures such as Nocturnal Temporal Lobe Epilepsy (NTLE) and in some cases of Nocturnal Frontal Lobe Epilepsy (NFLE). The latter could show mainly a sexualized pelvic thrusting as hyperkinetic features of the seizures. NTLE or NFLE could also presented with sexualized acts during epileptic discharges that are sexual hyperarousal, ictal sexual automatism and ictal orgasm. Video-PSG is mandatory to detect this abnormal behavior during sleep and the typical electrophysiological features in the cases of epilepsy.

Sleep-related painful erection is another form of parasomnia defined by the ICSD-2v as penile pain that occurs during REM-sleep related erection. This condition could determine frequent awakenings of the subject finally leading to a reduced sleep quality with a compliant of excessive daytime sleepiness. The erection and pain completely ceased as soon as patients awoke, while erections in the awaking state did not produce pain. Sometimes patients could present some genital abnormalities (such as Peyronie's syndrome) or neurological injuries (such as compression of the anterior hypothalamus), but in most cases there is no evidence of urologic or neurologic disease. Some patients may experience an increasing libido or sexual

activity in the effort to reduce or avoid the painful erection. Video-PSG shows reduced sleep efficiency with frequent awakenings during REM-sleep related erection [8].

Furthermore, some sexualized parasomnias are recognized in patients with brain injury or as clinical feature of psychiatric diseases. Hypersexuality in the transition from sleeping to waking is the most common sexual dysfunction in these patients. Moreover, sleep could exacerbate a condition of persistent sexual arousal syndrome, whereas the genital sensation and urges of achieving orgasm is not accompanied by any subjective sexual desire.

The linkage between parasomnia and sexuality is recently growing in importance for forensic implication in sexual abuse crime, especially in minor. Some legal defense in different crimes (especially homicide) are built upon the absence of full alertness or impairment of brain function related to sleep disorder. In the last years a large number of defendant's lawyers adopted the so-called "sleepwalking defense". This kind of defense is based on the scientific evidence of some NREM parasomnia predisposing, priming and precipitating factors in adults, especially in the subjects having a familiar and personal history of parasomnia. In the last years, this defensive line has been critically reviewed for the following two main considerations. Firstly, "the knowledge of a parasomnia with a low frequency of presentation in childhood is a physiological feature, becoming a disease only if it remains in adult age". Secondly "the set of circumstances resulting in a sexual misconduct during presumed parasomnia have to be extraordinary, unique and not ever more repeatable". Then, continuous sexual abuses made by a person aware of his parasomnia are legally culpable [9].

In 2002, Guilleminault et al. advised a flow-chart for the management of patients reported an abnormal sexual behavior during sleep or sleepsex. First of all, an extensive history of the patients should be performed including a detailed description of the event, exhaustive family and personal history with particular attention to sleep disorders such as parasomnia, habits like drug use or alcohol intake and psychiatric evaluation. Moreover, the history should be accompanied with interviews of bed partner or family members to highlight the description, frequency, nature (i.e. age of onset, stereotypical or not) of the event, attitude of the subject when awake or after a sleep-related event. A comprehensive neurological work-out, including EEG studies and video-PSG is useful to confirm the diagnosis and to avoid possible complex partial seizures potentially responsible for the behavior [10].

References

[1] Jankowski JT, Seftel AD, Strohl KP. Erectile dysfunction and sleep related disorders. J Urol. 2008 Mar;179(3):837-41. Epub 2008 Jan 25.

[2] Seftel AD, Strohl KP, Loye TL, Bayard D, Kress J, Netzer NC. Erectile dysfunction and symptoms of sleep disorders. Sleep. 2002 Sep 15;25(6):643-7.

[3] Luboshitzky R, Herer P, Levi M, Shen-Orr Z, Lavie P. Relationship between rapid eye movement sleep and testosterone secretion in normal men. J Androl. 1999 Nov-Dec;20(6):731-7.

[4] Karacan I. Erectile dysfunction in narcoleptic patients. Sleep. 1986;9(1 Pt 2):227-31.

[5] Koffel E, Watson D. Unusual sleep experiences, dissociation, and schizotypy: Evidence for a common domain. Clin Psychol Rev. 2009 Aug;29(6):548-59. Epub 2009 Jun 21.

[6] Driver-Dunckley ED, Noble BN, Hentz JG, Evidente VG, Caviness JN, Parish J, Krahn L, Adler CH. Gambling and increased sexual desire with dopaminergic medications in restless legs syndrome. Clin Neuropharmacol. 2007 Sep-Oct;30(5):249-55.
[7] Arnulf I, Zeitzer JM, File J, Farber N, Mignot E. Kleine-Levin syndrome: a systematic review of 186 cases in the literature. Brain. 2005 Dec;128(Pt 12):2763-76. Epub 2005 Oct 17. Review.
[8] Ferini-Strambi L, Oldani A, Zucconi M, Castronovo V, Montorsi F, Rigatti P, Smirne S. Sleep-related painful erections: clinical and polysomnographic features. J Sleep Res. 1996 Sep;5(3):195-7.
[9] Schenck CH, Arnulf I, Mahowald MW. Sleep and sex: what can go wrong? A review of the literature on sleep related disorders and abnormal sexual behaviors and experiences. Sleep. 2007 Jun 1;30(6):683-702.
[10] Guilleminault C, Moscovitch A, Yuen K, Poyares D. Atypical sexual behavior during sleep. Psychosom Med. 2002 Mar-Apr;64(2):328-36.

9.4. Other Neurological Diseases

Sexual disorders in chronic and disabling neurological diseases are common and underweighted symptoms. To our knowledge, sexuality in patients affected by polyneuropathies, motor neuron disorders and myopathies has been poorly reported so far.

The negative self-image and the fear of the partner's negative thoughts could cause insecurity and low interest in sex. Indeed, these patients are reluctant to approach sexual problems and consider these as another untreatable sign of the disease.

Disability may be an important trouble afflicting patients' moods. The most reported sexual disorder in these patients is loss of libido or orgasm disorders often psychogenic in origin and due to low self-esteem or scare of transmitting the hereditary disease to their offspring. However, genetic advances could improve these patients' sexual behavior: genetic counseling is growing in importance since prenatal and preclinical diagnosis could show the possibility, the predisposition and prevalence of genetic diseases, estimating the magnitude of recurrence risks, which is important for family planning (1, 2).

In *Amyotrophic Lateral Sclerosis (ALS)* sexual disorders are commonly associated with physical weakness and body changes. ALS patients may present a loss of strength in the pelvic muscle floor and a restricted pulmonary function that worsen sexual intercourse. Despite the reduction of all voluntary movement, neurophysiological tools don't show alteration in sexual reflexes so to lead to erection and ejaculation disorders. Indeed, many patients report masturbation and normal orgasm experiences. In a recent report, the most frequent sexual concerns were loss of libido, the patient's inhibition to show his/her body naked, and changes in couple relationship. The last problem seems related to the partner shifting from the role of lover to caregiver. The patient' s sexual passivity is another frequent reported condition leading to a reduced sexual behavior.

A decreased libido and erectile dysfunction might occur also in hereditary motor neuron diseases such as Kennedy's Syndrome (a X-linked bulbospinal muscular atrophy). In these patients altered sexual function is often associated with genital abnormalities such as testicular atrophy and gynecomastia [3].

In *Myopathies*, such as muscular dystrophy, sexual disorders seem to be the same as in ALS patients. The reduced strength of voluntary muscles could lead to a reduction of sexual behavior. The association with the psychological impact of a disabling condition can provoke an indifference to sexual activity. The scare of transmitting the disease to the children is the most important cause of loss of libido in patients presented with progressive muscular dystrophy. Good genetic counseling could improve the reproductive decisions in these patients improving their sexual behavior. In 1998 Egger and Zats reported the effect of clinical degree of disease and of recurrence risk on reproductive decisions in patients affected by Becker, limb-girdle and facioscapulohumeral muscular dystrophy. They found how the early onset, the disease severity and the past reproductive history could reduce reproductive outcome, while emotional/sexual dysfunctions seem to correlate with a reduction in family planning [2, 4].

Patients presented with *Polyneuropathies* refer a reduction of libido mainly related to the aforementioned psychopathological issues. An impairment of erection and ejaculation is also frequently reported. Neurophysiological tests may show an increased latency in penile dorsal nerve conduction and pudendal Somatosensorial Evoked Potential in association with aberrant bulbo-cavernosus reflexes. Moreover, the involvement of sensitive fibers may avoid the patient's use of condom causing an increasing risk to contract a sexually transmitted disease. In addition to the worry of procreating a sick offspring, the partner's refusal or inability to contraception may determine psychogenic anejaculation and orgasmic disorders.

Amyloid and rare inherited neuropathies may show urogenital symptoms as early manifestation. Dysautonomia related to small myelinated and unmyelinated nerve fiber involvement can lead to bladder and sexual dysfunction in these patients. A high incidental rate of erectile dysfunction is also observed in residual disability by Guillan-Barrè Syndrome.

Neuropathy in Diabetes Mellitus could present itself with sexual dysfunctions. Erectile dysfunction and retrograde anejaculation are the most reported sexual problem related to nerve dysfunction in diabetic patients. Erectile dysfunction in diabetic patients has many causes. Metabolic processes with variations in blood sugar concentration and acidosis may reduce cavernous tissue blood flow in association with the typical vascular damage of the small vessels. Atherosclerosis of dorsal penile artery is also frequent in diabetic patients. Moreover, pelvic muscle electromyography and pudendal nerve conduction analysis show a significantly higher rate of abnormalities in impotent diabetic males rather than potent diabetic men [1, 5, 6].

References

[1] Lundberg PO, Ertekin C., Ghezzi A., Swash M., Vodusek D. Neurosexology. guidelines for neurologists. european federation of neurological societies task force on neurosexology. *European Journal of Neurology*. 2001 2001;Sect. 8 (2-24).

[2] Eggers S, Zatz M. How the magnitude of clinical severity and recurrence risk affects reproductive decisions in adult males with different forms of progressive muscular dystrophy. *J. Med. Genet.* 1998 Mar;35(3):189-95.

[3] Wasner M, Bold U, Vollmer TC, Borasio GD. Sexuality in patients with amyotrophic lateral sclerosis and their partners. *J. Neurol.* 2004 Apr;251(4):445-8.

[4] Antonini G, Clemenzi A, Bucci E, Morino S, Garibaldi M, Sepe-Monti M, et al. Erectile dysfunction in myotonic dystrophy type 1 (DM1). *J. Neurol*. 2009 Apr;256(4):657-9.
[5] Rees PM, Fowler CJ, Maas CP. Sexual function in men and women with neurological disorders. *Lancet.* 2007 Feb 10;369(9560):512-25.
[6] Vinci P, Gargiulo P, Navarro-Cremades F. Sexuality in Charcot-Marie-Tooth disease. *Eura Medicophys.* 2007 Jun;43(2):295-6.

9.5. Major Psychiatric Diseases

Although sexuality is an important part of human life, sexual functioning in individuals with severe mental illness, such as schizophrenia, has received little attention. While patients may feel uncomfortable raising the subject because of cultural barriers or the mistrust of clinicians, the latter may be reluctant to discuss sexual concerns with their patients because they fear that sexual issues might exacerbate psychiatric symptoms or slow recovery, or may view sexual complaints as relatively minor when addressing symptoms associated with mental illness. The sexual response cycle can be affected by the illness itself or by medication. For some patients psychotropic treatment may improve sexual function secondary to the improvement of psychiatric symptoms; for other patients, psychoactive drugs may cause a worsening of sexual life. Male chronic mental patients are at higher risk of fathering unwanted children or of acquiring and transmitting sexual transmitted diseases. These patients have little access to health care, poor impulse control and judgment, and limited understanding of counseling messages. They are more likely to use illicit drugs, which are associated with high-risk sexual behavior, and to have short-term sexual encounters because of difficulty in maintaining stable relationships. Moreover, they may also engage in dangerous sexual behavior because of self-destructive suicidal or homicidal impulses. Interestingly, despite being at high risk of HIV infection, as a group, they are less likely to be tested for HIV. Several factors can disrupt sexual behavior in patients with major psychiatric disorders including biological factors, such as functional or structural alteration of cerebral regions mediating sexual behavior, psychopathological factors, poor social functioning, psychological factors, such as low self-esteem and social stigma, and side effects of drugs [1]. Limited existing data suggest that sexual dysfunction is common in patients with schizophrenia [2-5]. Indeed, it has been estimated that 30-60% patients with schizophrenia had sexual disorder with impairments in arousal and orgasm mainly reported in treated patients. Diminished libido, retrograde and spontaneous ejaculation, and priapism have also been described. The relation between sexuality and schizophrenia is complex. Since the illness presents at a young age, in parallel with the reproductive period onset, an alteration in the hypothalamic-pituitary-gonadal axis has been hypothesized. Indeed, lower levels of total gonadotropins and testosterone have been reported in un-medicated male with schizophrenia relative to controls. Most studies, however, have showed that conventional antipsychotic medications cause most of the sexual problems in schizophrenics through several mechanisms. Although it is important to examine the relationship between medication and sexual disturbances in schizophrenia patients, these patients may have underlying hormonal disturbances that preexist or contribute to sexual impairment. Medical comorbidity including

obesity, diabetes and cardiovascular disease, which are common in patients with schizophrenia, as well as concomitant medications, should be also taken into account. Moreover, lack of sexual activity may result directly or indirectly from low social confidence, few personal relationships, a loss of impulse control, and deficit symptoms such as lack of interest and anhedonia. One recent study found that sexual dysfunction in male patients with schizophrenia was associated with diminished quality of life, decreased occurrence of romantic relationships, and reduced intimacy when relationships are established [6]. Assessing sexual functioning in these patients is challenging. So far no single instrument or method to assess sexual functioning in patients with schizophrenia has been routinely used. Among several available instruments, the CSFQ (Changes in Sexual Functioning Questionnaire) has the advantages of being validated, gender specific, addressing phase-specific functioning and monitoring changes over time.

Similar to patients with schizophrenia, those affected by schizoaffective or bipolar disorder have a high frequency of sexual dysfunction, in particular hyposexuality manifesting as diminished sexual experience, sexual desire and performance with a consequent lessened interest in sexual activity or less access to sexual partners.

Borderline Personality Disorder is a complex mental illness characterized by a pervasive pattern of instability in emotion regulation, interpersonal relationships, self-image, and impulse control. Impulsivity affects multiple areas of life such as spending money, traffic behavior, substance abuse, eating, and sexuality. Clinical experience suggests that impulsive sexual behavior, identity disturbance, and unstable relationships accompanied by hyper- as well as hyposexual disorders (often leading to sexual avoidance or promiscuity) are frequently seen phenomena in borderline patients.

The ability to experience pleasurable, anxiety free mood states is vitally important for overall well-being with a consistent relationship between mental health, mental illness, and sexual functioning, and between sexuality and mood. In fact, one indicator of positively functioning mental health is a normal sexual expression, and rates of sexual dysfunction from 30% to 70% have been reported in depressed population [7-8]. Potentially, all phases of the sexual response cycle, with possible exception of resolution, are associated with depression; in addition, pain disorders are also found often in depressed people. Sexual desire disorders are common in up to 50% of people who are depressed, with the likelihood of a sexual desire disorder sometimes more than 5 times as likely in depressed than in non-depressed people. Disorders of arousal are also common either when assessed by subjective self report measures or by objective measures such as nocturnal penile tumescence. Nevertheless, so far none of these works has clearly established whether sexual dysfunction is caused by depression or if depression is caused by sexual dysfunction; rather than one causing the other, it seems likely that there are reciprocal and bidirectional effects of each type of dysfunction upon the other, or that they often appear together and are not easily separable.

A strong relationship exists between anxiety and sexual dysfunction, although it is not as clear as in depression. Generalized anxiety disorder appears to be associated with all phases of the sexual response cycle; obsessive compulsive disorder and panic disorder seem to be primarily associated with lowered sexual desire and sexual aversion, although lower arousal, pain, and reduced satisfaction have also been noted. Social phobia also appears to be related to lower sexual desire and to premature ejaculation, while post-traumatic stress disorder, in individuals with a history of sexual abuse, is often linked to sexual avoidance, hyposexuality, and sometimes hypersexuality.

References

[1] Raja M, Azzoni A. Sexual behavior and sexual problems among patients with severe chronic psychoses. *Eur. Psychiatry*. 2003 Mar;18(2):70-6.

[2] Fan X, Henderson DC, Chiang E, Briggs LB, Freudenreich O, Evins AE, Cather C, Goff DC.Sexual functioning, psychopathology and quality of life in patients with schizophrenia. *Schizophr. Res.* 2007;94:119-27

[3] Kelly DL, Conley RR. Sexuality and schizophrenia: a review. *Schizophr. Bull*. 2004;30:767-79.

[4] Westheide J, Helmstaedter C, Elger C, Cooper-Mahkorn D, Sträter B, Maier W, Kühn KU. Sexuality in male psychiatric inpatients. a descriptive comparison of psychiatric patients, patients with epilepsy and healthy volunteers. *Pharmacopsychiatry*. 2007;40:183-90

[5] Mosaku KS, Ukpong DI.Erectile dysfunction in a sample of patients attending a psychiatric outpatient department. *Int. J. Impot. Res.* 2009;21:235-9

[6] Olfson M, Uttaro T, Carson WH, Tafesse E. Male sexual dysfunction and quality of life in schizophrenia. *J. Clin. Psychiatry.* 2005;66:331-8.

[7] Laurent SM, Simons AD. Sexual dysfunction in depression and anxiety: conceptualizing sexual dysfunction as part of an internalizing dimension. *Clin Psychol. Rev.* 2009;29:573-85.

[8] Nicolosi A, Moreira ED Jr, Villa M, Glasser DB.A population study of the association between sexual function, sexual satisfaction and depressive symptoms in men. *J. Affect Disord.* 2004;82:235-43

9.6. Iatrogenic Sexual Dysfunction

Drug-induced sexual dysfunction (SD) is a common problem occurring during treatment of a variety of illnesses, including depression, schizophrenia, hypertension and diabetes mellitus. *Antidepressants*, among all psychotropics, are most likely to cause SD, and orgasm disturbances (delayed ejaculation or anorgasmia) are the type most commonly associated with them [1-2]. The association of antidepressants and decreased libido must be viewed cautiously, since 50% to 90% of untreated patients with depression experience decreased libido [3]. In fact, many patients with depression experience increased libido when they are successfully treated with an antidepressant. Similarly, although antidepressants have been reported to cause arousal disturbances, erectile dysfunction is more likely to be related to depression or secondary to drug-induced ejaculatory delay. Indeed, the relationship between sexual dysfunction and depression seems to be bidirectional, in that the presence of either one of these conditions may trigger or exacerbate the other, and the treatment of one condition may improve the other. Treatment-emergent SD can be an added source of distress for patients with depression, which, if left untreated, may prolong or worsen the illness, compromise treatment outcome, affect quality of life, and lead to noncompliance with treatment. The overall prevalence rate of SD in medicated patients with major depressive disorder is estimated to be more than 50% (4). *Tricyclic antidepressant* (TCA)-related SD is particularly high, although the lack of available standardized assessment measures, when

these drugs were in development, limits comparison with current agents. Limited evidences suggested that amitriptyline, clomipramine and imipramine are more often associated with alterations in orgasm, desire and even arousal. Among monoamine oxidase inhibitors, *moclobemide* is associated with low incidence of SD (5).

Selective serotonin reuptake inhibitors (SSRIs) have been associated with adverse effects on all three phases of sexual function, although their most prominent effect is delayed orgasm/ejaculation and anorgasmia. SSRIs have also been reported to cause decreased libido. The consensus from a series of well-designed comparative studies is that up to 60% of patients receiving SSRIs report some form of treatment emergent SD [5, 6, 7]. Interestingly, in a recent large series of patients with SD, the use of SSRIs, but not other antidepressants or benzodiazepines, negatively affected almost all the components of the sexual response cycle. Moreover, the use of SSRIs was associated with a mild hyperprolactinemia. The effects of SSRIs on arousal and orgasm may be mediated by stimulation of serotonergic projections from medullary raphe nuclei to the spinal cord. The decrease of libido may be due to decreased dopaminergic activity mediated by stimulation of serotoninergic projections from midbrain raphe nuclei to the mesolimbic dopamine system. In particular, although these effects seem to be related to the stimulation of serotonin, especially on 5HT2 receptors, other mechanisms are likely to be involved. For example, the high rate of SD associated with paroxetine (i.e. anorgasmia and erectile dysfunction) may be attributed also to cholinergic receptor blockade and nitric oxide synthase-inhibiting effects.

Reboxetine, a norepinephrine transporter inhibitor (NRI), has demonstrated superiority in sexual function outcomes compared with different SSRIs (i.e. citalopram, paroxetine and fluoxetine). There is some evidence that noradrenergic effects may mitigate the serotonin influence on sexual function. Indeed, treatment-emergent SD with duloxetine and venlafaxine, two common *serotonin noradrenaline reuptake inhibitor*s (SNRIs), has been demonstrated to be significantly lower, when compared with other SSRIs. Mirtazapine-induced SD are significantly less common than with SSRIs, SNRI, and TCA. *Mirtazapine* stimulates noradrenergic and serotoninergic activity through its agonist effect on postsynaptic receptor 5-HT_{1A} and concurrent antagonist effect on 5-HT_2 and 5-HT_3 receptors; the 5-HT_2 blockade prevents serotonin –mediated adverse effects on sexual function.

With its dual inhibition of norepinephrine and dopamine reuptake, *bupropion* is devoid of any direct effects on the serotonin system and has the potential to positively affect arousal and desire. In fact, it has been demonstrated that bupropion resulted in less SD than fluoxetine, paroxetine, or sertraline, with regard to orgasm dysfunction [8]. SD is considered as one of the most common reasons for patients' dropping out of treatment with antidepressant. Patients should be counseled about the potential for antidepressant-induced changes in their sexual function and told that such changes can be managed. Options include waiting for tolerance to develop, decreasing the dosage, giving drug holidays, augmenting therapy with an additional drug, and switching to an alternative antidepressant less likely to cause SD. Nevertheless, no trials assessing management for antidepressant-induced SD were found showing a benefit of psychological interventions, mechanical devices, or changes to antidepressant medication regimen [9]. There is some evidence that for men with antidepressant- induced ED, the addition of sildenafil is of benefit in improving sexual function, while at the present, it is unclear if the addition of bupropion or buspirone is of benefit.

There are only sporadic reports of the impact of *mood stabilizing agents* on sexual function. *Lithium carbonate* resulted in reduced sexual interest and increased erectile

difficulties in 20% of bipolar and schizoaffective male patients, although there was no correlation between lithium level and loss of overall satisfaction during sexual activity.

Many *anticonvulsivants*, such as *carbamazepine* and *valproate*, are commonly used as mood stabilizers and, as better specified in a previous chapter, they may lead to SD through complex and still poorly understood mechanisms [10].

Benzodiazepines (BDZ) act to increase the inhibitory process of the central nervous system primarily though γ-aminobutyric acid, a chief inhibitory neurotransmitter. Although the overall risk of SD with BDZ is relatively low, high dose BDZ therapy has been associated with an increased incidence of SD. In contrast, anxiolytics which act primarily on 5-HT1A, such as *buspirone*, are associated with improved sexual function.

Decreased libido is very common with the *older* conventional *antipsychotic drugs* (e.g., haloperidol, fluphenazine, and chlorpromazine), since they are potent dopamine blockers also increasing prolactin levels, with 30% to 60% of patients experiencing disturbances in sexual function [11-12]. Among the newest atypical antipsychotic drugs, *risperidone* is most likely to cause elevations in prolactin levels and hyperprolactinemic symptoms such as gynechomastia , erectile dysfunction, and decreased libido. On the contrary, hyperprolactinemia is rarely associated with quetiapine, ziprasidone, aripriprazole, or clozapine [11]. Moreover, risperidone has also been associated to ejaculatory dysfunction, such as retrograde ejaculation [13]. Interestingly, because of their increased serotoninergic effects, atypical antipsychotics may cause additional adverse effects on arousal and orgasm function.

Beyond psychotopics, many other drugs, such as antihypertensives (especially hydrochlorothiazide and propanolol), cimetidine, amiodarone, may impair sexual function.

Beside the aforementioned drug-induced SD, even surgery may cause iatrogenic SD.

Surgical techniques for primary cancer are designed to excise the tumour beyond its margins to mitigate regional tumour spread. However, because the autonomic nerves are intimately related to the structures within the surgeon's operative field, damage to these nerves and subsequent SD has been regarded as an inevitable part of radical surgery for cancer of prostate, bladder and rectum. When pelvic autonomic innervations are bilaterally disrupted, PDEis can have no benefit as their action depends on some neural integrity to supply a minimum of nitric oxide neurotransmitter. Nerve-sparing surgical techniques are promising, and their benefits for sexual function have been proved by some authors [14].

References

[1] Stimmel GL, Gutierrez MA. Sexual dysfunction and psychotropic medications. *CNS Spectr*. 2006;11(8 Suppl 9):24-30.

[2] Gregorian RS, Golden KA, Bahce A, Goodman C, Kwong WJ, Khan ZM. Antidepressant-induced sexual dysfunction. *Ann. Pharmacother*. 2002;36:1577-89.

[3] Rosen RC, Lane RM, Menza M. Effects of SSRIs on sexual function: a critical review. *J. Clin. Psychopharmacol*. 1999;19:67-85

[4] Kennedy SH, Rizvi S. Sexual dysfunction, depression, and the impact of antidepressants. *J. Clin. Psychopharmacol*. 2009;29:157-64.

[5] Montejo AL, Llorca G, Izquierdo JA, Rico-Villademoros F.Incidence of sexual dysfunction associated with antidepressant agents: a prospective multicenter study of 1022 outpatients. Spanish Working Group for the Study of Psychotropic-Related Sexual Dysfunction. *J. Clin. Psychiatry.* 2001;62 Suppl 3:10-21.

[6] Corona G, Ricca V, Bandini E, Mannucci E, Lotti F, Boddi V, Rastrelli G, Sforza A, Faravelli C, Forti G, Maggi M. Selective serotonin reuptake inhibitor-induced sexual dysfunction. *J. Sex Med*. 2009;6:1259-69.

[7] Werneke U, Northey S, Bhugra D. Antidepressants and sexual dysfunction. *Acta Psychiatr. Scand.* 2006;114:384-97.

[8] Thase ME, Haight BR, Richard N, Rockett CB, Mitton M, Modell JG, VanMeter S, Harriett AE, Wang Y. Remission rates following antidepressant therapy with bupropion or selective serotonin reuptake inhibitors: a meta-analysis of original data from 7 randomized controlled trials. *J. Clin. Psychiatry*. 2005;66:974-81.

[9] Taylor MJ, Rudkin L, Hawton K. Strategies for managing antidepressant-induced sexual dysfunction: systematic review of randomised controlled trials. *J. Affect. Disord.* 2005;88:241-54.

[10] Aizenberg D, Sigler M, Zemishlany Z, Weizman A. Lithium and male sexual function in affective patients. *Clin. Neuropharmacol*. 1996;19:515-9

[11] Bostwick JR, Guthrie SK, Ellingrod VL. Antipsychotic-induced hyperprolactinemia. *Pharmacotherapy*. 2009;29:64-73.

[12] Westheide J, Cohen S, Bender S, Cooper-Mahkorn D, Erfurth A, Gastpar M, Huber TJ, Maier W, Murafi A, Rothermund M, Signerski J, Sträter B, Teusch L, Weig W, Welling A, Kühn KU. Sexual dysfunction in psychiatric inpatients the role of antipsychotic medication. *Pharmacopsychiatry*. 2007;40:140-5

[13] Loh C, Leckband SG, Meyer JM, Turner E. Risperidone-induced retrograde ejaculation: case report and review of the literature. *Int. Clin. Psychopharmacol*. 2004 Mar;19(2):111-2

[14] Pace G, Rosso AD, Vicentini C. Penile rehabilitation therapy following radical prostatectomy. *Disabil. Rehabil*. 2010 Feb 15. [Epub ahead of print]

In: Male Sexual Dysfunctions in Neurological Diseases… ISBN 978-1-61761-855-0
Editor: Calabrò Rocco Salvatore

Chapter 10

Treatment and Rehabilitation of Sexual Dysfunctions in Neurological Diseases

Rocco Salvatore Calabrò, Anna Furnari and Placido Bramanti
IRCCS Centro Neurolesi "Bonino-Pulejo", Messina, Italy

Abstract

Since sexual dysfunction is very common in male affected by neurological diseases, it is mandatory that neurologists are aware of sexual problems and of their treatment in order to improve patient's quality of life. Erectile dysfunction (ED) is a highly prevalent problem increasing with age, as well as the major men's sexual concern. Significant advances in the pharmacologic treatment of ED have occurred in recent years, most notably after the introduction of sildenafil, the first oral selective phosphodiesterase type 5 inhibitor. Nevertheless, many other oral, local and surgical treatments are available and their efficacy and safety depend on the specific cases. Also disorders of desire and orgasm may affect neurological patients and the proper treatment is herein discussed in order to help physician in patient management. Also rehabilitation techniques, including neurosurgical treatment for erection and anejaculation, are described in this chapter.

Introduction

Significant advances in the understanding of the physiology and pathophysiology of male sexual function, and in methods of its investigation and treatment, have been attained during the past decades. Since sexual dysfunction is very common in male affected by neurological diseases, it is mandatory that neurologists are aware of sexual problems and of their treatment in order to improve patient's quality of life.

Sexual counseling is an important part of the rehabilitation strategy of neurological disorders. Indeed, the first step is to let the patient know that is permitted to discuss sexuality in the clinical setting. After giving essential information about sexual physiology and

practical issues that are pertinent to a person with particular symptomatology and handicap in question, a specific therapy may be proposed.

This chapter is aimed at elucidate the available treatment options of neurogenic sexual disorders, with regards to pharmacological therapy and rehabilitation techniques.

1. Erectile Dysfunction

Erectile dysfunction (ED) is a highly prevalent problem increasing with age, as well as the major men's sexual concern. ED shares common risk factors with cardiovascular diseases, i.e. diabetes mellitus, dyslipidemia, smoking, hypertension, absence of physical exercise and obesity.

Moreover, ED is associated with a high incidence of depressive symptoms and has a profound negative impact on the quality of life of patients and their partners. Neurologic erectile dysfunction can be broadly defined as an inability to sustain or maintain a penile erection owing to a neurologic impairment, both centrally and peripherally.

Oral pharmacotherapy is currently the mainstay of treatment for ED. Although a number of oral prescription drugs may have the potential to be used to treat impotence, most of these drugs act centrally, they are not so effective in this regard and have a number of side effects.

Significant advances in the pharmacologic treatment of ED have occurred in recent years, most notably after the introduction of sildenafil, the first oral selective phosphodiesterase type 5 (PDE5) inhibitor, in 1998. Sildenafil quickly gained acceptance by the medical community and the public because of its broad efficacy for different types of ED and its ease of use. Two PDE5 inhibitors, vardenafil and tadalafil, have since joined sildenafil to compete in the ED market [1]. *Sildenafil* is a potent and selective inhibitor of the catalytic site of the phosphodiesterase 5 (PDE5), an enzyme that hydrolyses cyclic GMP (cGMP). When a man is sexually aroused, cGMP synthesis in penile vascular smooth muscle increases and accumulates in healthy individuals; if sildenafil (or vardenafil and tadalafil) is present, PDE5 catalytic activity will be blocked and cGMP accumulation will be enhanced in the penile tissues. The resulting increase in intracellular cGMP activates the cGMP-dependent protein Kinase finally leading to a lowering of cytosolic Ca^{2+} and relaxation of the vascular smooth muscle of penile arteries and corpora cavernosa [2]. Interestingly, action of PDE5 inhibitors (PDE5i) to improve erection requires sexual arousal in order to increase nitric oxide (NO) release from nerve terminals in the penile vasculature. Several studies have been published exploring the efficacy and safety of PDE5i in patients with diabetes, hypertension, cardiovascular diseases, depression, kidney and liver diseases and different neurological disorders such as spinal cord injury (SCI) and multiple sclerosis (MS) [3-4-5]. A recent study by Lombardi et al [5] showed that sildenafil is efficient and well-tolerated in the long term treatment (i.e.10-year-follow-up) for ED caused by SCI. Another study by the same authors[4] demonstrated that tadalafil seems to be a practical option in minimizing ED and increasing QoL for men with MS. PDE5i Have limited contraindications, including concomitant use of nitrates, patients with a history of retinitis pigmentosa or diseases predisposing to priapism such as leukemia or multiple myeloma. Moreover, attention may be paid to those patients who demonstrate hemodynamic instability while receiving α-blockers alone, since they are at increased risk of symptomatic hypotension with concomitant use of

PDE5i. Common adverse events with all three PDE5i include headache, flushing, nasal congestion and dyspepsia. Specific drug-related adverse effects include visual disturbance, mainly for sildenafil and vardenafil, and myalgia/back pain, mainly for tadalafil. However, these adverse events are generally mild, self-limited after long-term use and not associated with treatment discontinuation. Lastly, the possible relationship between non-arteritic anterior ischemic optic neuropathy (NAION) and PDE5i use has raised important questions; nevertheless, to date, there is no epidemiological evidence that the incidence of NAION is higher in patients receiving PDE5i [6].

Of particular recent interest has been the utilization of PDE5i as routinely dose medication. Based on existing animal data, it has been hypothesized that administration of daily PDE5i may help to prevent apoptosis in the corporal sinusoids, preserve smooth muscle content, and reduce collagen accumulation in a variety of disease states. Therefore, routine dose PDE5i has been investigated as means for long-term modulation and treatment of ED (typically Ed related to cavernous nerve or corporal tissue damage), stuttering ischemic priapism, and some lower urinary tract symptoms. Although several small studies have supported daily low-dose sildenafil for penile rehabilitation, the largest trial to date has suggested no erectile function benefit from routine dose vardenafil. Thus, in the absence of a large studying demonstrating clear long-term benefit from daily use of PDE5i for penile rehabilitation, this form of therapy should still be considered investigational [7].

A variety of new PDE5i with promising pharmacokinetic properties, i.e. avanafil, udenafil, lodenafil, mirodenafil and SLx2101, are in development for the management of ED in humans.

Patients with severe neurological damage, post-radical prostatectomy, severe vascular disease may not respond to PDE5i, probably due to a decreased expression or activity of neural or endothelium NO synthase. When novel dosing strategies are not effective in optimizing the efficacy of PDE5i in these specific cases, other treatment options should be considered (see table 1).

Phentolamine. Phentolamine induces relaxation of corpus cavernosum erectile tissue by direct antagonism of both α_1 and α_2 adrenergic receptors and by a possible indirect activation of the NO synthesis. To date, phentolamine has been used mainly as an adjuvant to other intracavernous vasoactive agents. However, its effectiveness in the management of erectile insufficiency, at an oral dose of 40-80 mg, has been suggested in recent limited studies, reviewed by Goldstein (8). Although the drug is associated with possible severe adverse events, the most common described side effects are nasal congestion, headache, dizziness and tachycardia [9-10].

Yohimbine. Yohimbine facilitates erection by blocking central α_2 adrenergic receptors and produces an increase in sympathetic drive and firing rate of neurons within the brain noradrenergic nuclei. It has been demonstrated that this centrally-acting drug (up to 6 mg) is superior to placebo in the treatment of ED, even if, in generally, available results on treatment are not impressive. Moreover, in a pilot study yohimbine has been shown to improve antidepressants-induced impotence. The reported side effects, when this drug is used for purpose other than ED, include increases in heart rate and blood pressure, orthostatic hypotension, anxiety, agitation and manic reactions, but the side effects observed in ED patients are usually mild [9-10].

Table 1. Therapeutic approaches to erectile dysfunction of organic causes

I. Oral and topical pharmacoptherapy
A. CENTRAL AGENTS
- *Adrenergic receptor antagonist*
  - Phentolamine
  - Yohimbine
  - Delquamine
- *Dopaminergic receptor agonist*
  - Apomorphine
  - Bromocriptine
- *Serotoninergic receptors antagonist*
  - Trazodone

B. PERIPHERALLY ACTING AGENTS
- Phosphodiesterase-5 inhibitors (sildenafil or other)
- Nitrogliceryne
- l-Arginine
- Minoxidil

II. Intracavernosal therapy
- Papaverine
- Papaverine-phentolamine mix
- Prostaglandine E1
- Trimix (Papaverine-Phentolamine-Prostaglandine E1)
- Calitonine Gene-related Peptide (CGRP)

III. Penile vascular surgey

IV. Penile prosthesis

V. Penile vacuum devices

Apomorphine. Apomorphine is a non selective dopamine agonist with moderate efficacy and good tolerability in the treatment of mild ED. Interestingly, stimulation of the dopamine D2 receptors located in the medial preoptic area of the hypothalamus may induce penile erection in rats, while D1 receptors are believed to have the opposite effect. Apomorphine may be considered a valid alternative ED treatment either when injected subcutaneously or when sublingually assumed (the sublingual formulation 2 and 3 mg have recently led to approval for clinical use in several countries). The drug may be used as an adjunct to sildenafil in patients who are minimally responsive to single-agent therapy, or for whom a lower dose of sildenafil may be necessary, secondary to cardiovascular comorbidities. Apomorphine is associated with bradycardia, dizziness and syncope, whereas nausea is the

most common adverse event with the paraventricular nucleus as the main neuroanatomical substrate of this effect [11].

Naltrexone. It is well documented that chronic injection of opioids can lead to decreased libido and impotence, possibly due to hypogonadotropic hypogonadism. Assuming that endogenous opioids may be involved in sexual dysfunction, opioid antagonists, such as naltrexone, have been suggested to be effective as a treatment for ED. Indeed, it has been shown that naltrexone increased the frequency of morning erection and successful coital attempts [12].

Trazodone. Trazodone is an atypical antidepressant drug, which selectively inhibits central 5HT uptake and increases the turnover of brain dopamine. It is likely that major therapeutic effects of trazodone on libido and erectile function is mostly mediated through the stimulation of 5HT1c receptor and, possibly, through α-adrenoceptor blockage leading to a subsequent reduction in the sympathetic tone. Its therapeutic use for management of ED remains controversial, although it has been demonstrated to restore erectile function in up to 60% of the patients and, anyway, the drug may be a valid alternative in some anxious and depressed men.

Dietary supplements. Men have relied on dietary aids to alleviate andrologic disorders for century and across cultures. Several dietary supplements and nutraceuticals worldwide used not only have purported benefits on erectile function, but also on the cardiovascular system in general [13]. This mirrors recent findings that erection and cardiovascular health are not only affected by the same risk factors, but that impotence is frequently a precursor of cardiovascular disease. Thus, this supplements maybe used in those patients with associated vascular and neurologic sexual dysfunctions. *L-arginine* is a nitric oxide (NO) donor for neural and endothelial NO-synthase increasing NO production when consumed in supraphysiologic doses of more than 3 g per day. NO plays a central role in mediating erection trough vasorelaxation, by way of increased levels of cyclic guanosine monophosphate and decreased calcium levels in vascular smooth muscle cells. To boost NO levels, L-arginine is often combined with the NO-synthase stimulant pygnogenol, a pine bark derivative, and this combined approach seems to be effective even in human ED. Although *ginkgo biloba* has been used more frequently to improve cerebrovascular microcirculation, its central effect have been postulated to ameliorate antidepressant-induced ED. Of the different varieties of ginseng which are frequently found in dietary supplements, Korean Red Ginseng has been most extensively studied in relation to Ed with inconsistent results. Finally, an improvement of erectile function has been described with L-carnitine, which acts through a prostaglandin-induced vasorelaxation of arterioles.

Local Therapies

Injectable and intraurethral agents were relegated to second line therapy after the appearance of the effective oral PDE5i. However, the local delivery of medication remains useful as in about 25-30% of ED patients PDE5i are ineffective [14,15].

Papaverine. Intracavernosal papaverine injection was the first clinically effective pharmacological therapy for ED. Papaverine is an opium alkaloid which acts as a non specific phosphodiesterase inhibitor with an increase in intracellular cAMP and cGMP leading smooth muscle relaxation and penile erection. Injections of the drug alone produce a full erection

(lasting from 30 min to more than 240) in about 35-55% of patients, depending on dose used (from 3 mg to more than 100 mg) and the underlying pathology. Patients with underlying arterial disease tend to require higher doses with a low rate of sexual response, while patients with neurological disease require small amounts and experience a more lasting response. Papaverine systemic side effects may include hypotension with reflex tachycardia, peripheral vasodilatation, elevation in liver enzyme; local adverse effects are fibrosis and priapism, the latter occurring more frequently in patient with neurological and psychological disease.

PGE1. PGE1 is a potent smooth muscle relaxant and vasodilator in man, acting via activation of EP prostaglandin receptors that results in an increase in the intracellular concentration of cAMP. It also has an α_2 adrenergic blocking effect and hence has the potential of reducing sympathetic overtone in patients with psychogenic ED. Intracavernosal PGE1 is licensed for the treatment of men with ED and its efficacy was largely demonstrated [16]. The most common adverse event is penile pain, while prolonged erection occurs in about 5% of the patients.

Vasoactive Intestinal Polypeptide and Phentolamine. Vasoactive intestinal peptide (VIP) is a neurotransmitter which exerts regulatory actions on blood flow, secretion and muscle tone. VIPergic nerves are most densely concentrated in the penis around the pudendal arteries and in the erectile tissue of the corpus cavernosum. VIP has been shown to elevate cAMP intracellular concentrations without affecting cGMP levels. The first instance of the use of VIP as intracavernosal injection monotherapy for ED was disappointing and it has shown more promise when used in combination with phentolamine, which may facilitate penile erection by inhibiting the functional predominance of α_1 receptor activity that maintains erectile tissues in a flaccid state [17].

Combinations. Phentolamine, papaverine, PGE1, and VIP are the vasoactive agents most commonly used in combination therapy of ED. This treatment is not only predictably more efficacious as a result of well-planned strategies based on sound pharmacological principles but it is also associated with a reduction in incidence of side effects and cost per dose.

Both PGE1 (alprostadil) and PGE2 (dinoprostone) are used as intraurethral treatments of erectile insufficiency. Medicated urethral system for erection *(MUSE)* is a licensed alternative way to deliver alprostadil to corporal bodies. MUSE involves the insertion of a delivery catheter into the meatus depositing an alprostadil pellet in the urethra so that the drug is absorbed through the urethral mucosa. The efficacy and tolerability of MUSE has been widely demonstrated, even if intracavernosal alprostadil is considered more effective.

Although there has been considerable interest in the potential use of topical agents applied to the skin of the penis, the clinical results have been disappointing so far. Indeed, achieving a functional erection with topical application of vasoactive drugs has been limited, but with more success in patients with psychogenic and neurogenic disorders than in those with vascular diseases. Vasodilating agents topically used include nitrates, PGE1, papaverine, minoxidil, aminophylline, and co-dergocrine [10].

Non Surgical Devices

Vacuum constriction device. The device usually consists of a wide clear plastic barrel that is placed around the penis and sealed against the pubic region. It provides passive engorgement of the penile tissue through the generation of an increasing negative pressure in

the cavernous sinusoidal spaces, in conjunction with a constrictor ring placed in the root of the penis to retain blood within the corpora cavernosa. Generally, these devices are used as a non invasive method of treatment for patient with vascular and neurogenic ED. The only contraindications are bleeding disorders and anticoagulation therapy. Pain, inability to ejaculate, and numbness are the most common adverse event, while skin necrosis can be avoided removing the constriction ring within 30 minutes. Efficacy rates (i.e. erection satisfactory for intercourse) as high as 90% have been described regardless of ED etiology.

Constrictive ring. The constrictive ring is likely to be the only external device needed for management of ED in patients with mild to moderate venous leakage and no coexisting significant arterial insufficiency.

Surgical Treatment

About 40% of patients with ED have evidence of abnormal arterial flow, only partly involving aortoiliac carrefour, since most men with major vessel disease rarely present with impotence. Conversely, the majority of vascular ED patients have pathological changes in the small vessels of the penis and, generally, *revascularization* for such smaller arteries is challenging with long-term patients' dissatisfaction and complications including pain, altered sensation, shortening of penile length and glans hyperemia. Also the long-term success rate of *penile vein ligation* is poor. *Penile prosthesis* offers a valid therapeutic alternative for patients who fail vasoactive drugs and vacuum-constrictive devices and who are not candidates for vascular reconstruction procedures. Devices are placed by creating an adequate space within both cavernosal bodies, followed by implanting a prosthetic erectile element. The two erectile elements are linked to a pump that is implanted into the scrotum, and to a fluid reservoir that is located into the scrotum, the pelvis or the abdominal cavity. Several factors have to be taken into account when selecting one of the different marketed devices, including penile size, presence of intracorporeal fibrosis, and the expectation of the patient and his partner. Possible complications are device failure, penile shortening, and infections. The development of microsurgical techniques and free tissue transfers hold to promise of success for *phallic reinnervation*, whereas the major sensory nerve of the donor free flap is usually coapted to the pudendal nerve. Unfortunately, this procedure is mainly performed as a part of the total phallic reconstruction in patients with micropenis, penile trauma or in female-to-male transsexual conversion so far [10; 15].

Future Treatment

- *Bremelonotide*. It is a synthetic peptide analogue of α-melanocite stimulating hormone (α-MSH) and is am antagonist of melanocortin receptors 3 and 4. The effects of α-MSH on sexual behavior, including grooming, stretching, yawing and penile erection, have been demonstrated in laboratory animals. Melanotan II as subcutaneous injection was shown to induce penile erections in patients with psychogenic and/or organic ED.

- *Glutamate receptors agonists*. Hippocampal glutamate ionotropic receptors may play a significant role in initiation of penile erection. In rat model, hippocampal of glutamate receptor subtype agonists produced multiple episodes of intracavernosal pressure.
- *Serotonin receptors agonists*. It is well known that serotonin exert a general inhibitory effect on male sexual behavior, although the amine may be inhibitory or facilitatory depending upon actions at different sites and on different serotonin receptors. RSD 992, an agonist at 5-HT2c receptors, induced erections and facilitated male copulative behavior, suggesting an important role for this receptor in the control of erectile mechanisms.
- *Rho-Kinase inhibitors*. There is considerable activity of rho-kinase in the human erectile tissue, and inhibition of rho-kinase mediated functions relaxes erectile tissue in vitro. Topical application of a rho-kinase inhibitor produced erectile responses in rodents.
- *Gene therapy*. The application of gene therapy for ED represents an exciting new field, which may effectively restore or supplement defective function and/or antagonize the expression of a mutant gene. Local gene therapy, as shown in preclinical studies, represents a viable treatment option for ED in diverse pathological conditions, including aging, diabetes, dyslipidemia, and cavernous nerve injury.
- *Tissue Engineering.* This new technique is being currently investigated for reconstructing penile tissue or treating ED, although currently tissue engineering belongs to the field of basic research. Nevertheless, new research is underway, in particular, on phallic reconstruction and tunica tissue for reconstruction of severe cases of Peyronie's disease. [2;15].

2. Disorders of Ejaculation

A. Premature ejaculation

Since premature ejaculation (PE) is mostly due to a psychogenic etiology, *psychosexual treatment* is considered the mainstay with high rates of success. Nevertheless, it has been shown that the failure of psychosexual-behavioral therapy, such as the stop-start technique and the start-stop-squeeze by Master and Johnson, may be related to the pooled patients with different PE categories, age groups, anxiety level, sexual experience and somatic vulnerabilities (i.e. urologic and neurogenic hypersensitivities), investigated in many of the studies.

Extending the ejaculation time is a common side effect of many antidepressants, which therefore can be used in PE continuously and at a low dosage or just on-demand. The tricyclic *antidepressants* such as clomipramine, and the selective serotonine reuptake inhibitors (SSRI), such as paroxetine, are the most common and effective drugs used in PE. Indeed, they promote serotonin activities though the inhibition of its reuptake and especially clomipramine seems to increase the sensory threshold for stimuli in the genital area, possibly through

inhibition of the adrenergic receptors in the peripheral sympathetic system. The use of α adrenergic receptor blockers to delay PE is based on the understanding that sympathetic nervous system is the responsible for the peristaltic movements of the seminal fluid through the male genital tract. Preliminary studies have confirmed the effectiveness of these agents in PE, but large well controlled trials should be fostered to examine both efficacy and safety of long-term use. In some cases, *local anesthetics* can be used. Generally, anesthetic creams are applied to the glans penis and penile shaft under occlusive cover (condom) for at least one half-hour before the sexual intercourse. Dermal analgesia reaches its maximum at 2-3 h, and persists for 1-2 h after removal [10,15,18,19]. To date, the only drug regularly approved for the treatment of PE is *dapoxetine*, which has been shown to be effective in several large clinical trials. The drug has the shortest half-life of all SSRIs, which is claimed to account for its failure as an antidepressant and optimal profile in PE. It may be assumed therefore that the clinical utility of dapoxetine is the consequence of the acute elevation of 5-HT on each occasion the drug is taken 'on demand' [20].

B. Anejaculation/Anorgasmia

Since the most common etiology of anorgasmia is the intake of psychotropic agents, regaining of the orgasmic sensation may be achieved with discontinuation and/or substitution of the incinting drug.

In cases of anejaculation, vibratory stimulation may be helpful, but intact dorsal penile nerves are necessary for the ejaculatory response. If the aim is to retrieve sperm for assisted fertilization, electroejaculation is preferred, as better specified in the above section.

Interestingly, a recent study showed that autonomic stimulation with midodrine enhanced orgasm rate, in spinal cord injured men, mainly by creating anterograde ejaculation [21].

C. Painful Ejaculation

Ejaculatory pain represents a component of sexual dysfunction that has received little attention in the literature so far. Postorgasmic pain is associated with prostatitis**,** chronic pelvic pain syndrome, benign prostatic hyperplasia, ejaculatory duct obstruction, prostate radiation, and radical prostatectomy. Different etiopathogenetic theories have been postulated including bladder neck closure after radical prostatectomy, ejaculatory duct stones, antidepressant medication, and compressive pudendal neuropathy. The treatment options vary from self-care to medication with alpha-blockers such as tamsulosin, antidepressants such as amitriptilyne, antiepileptics, antinflammatory agents and muscle relaxants, and even surgical procedures such as pudendal nerve decompression. We have recently described an unusual case of painful ejaculation due to spinal cord injury dramatically improved after topiramate administration; a central sensitization of the central pattern generator for ejaculation was supposed by the authors [22]. Nevertheless, since post-ejaculation pain is often psychogenic, treatment relies entirely on psychosexual and behavioral intervention, but patients who are severely anxious and unable to relax may benefit from a benzodiazepine agent.

3. Priapism

Prolonged erection may be a side effect of intracorporeal injection and, less frequently, can be associated with systemic drug intake such as phenotiazine and trazodone. Mild cases may be treated with oral intake of α-receptor agonists such as pseudoephedrine. More severe cases of priapism lasting for more than 4 h usually require corporeal aspiration and irrigation with a solution of heparin and epinephrine. Occasionally, prolonged priapism (of more than 24-36 h duration) requires surgical placement of an arterio-venous shunt, which will cause a venous leakage and a possible failure of response to future vasoactive drugs.

Interestingly, cocaine-induced priapism can be a high flow variant that is refractory to therapy and may require shunt placement or even partial penectomy.

4. Abnormal Sexual Desire

A. Hypoactive or Deficient Sexual Desire

It is well known, that primary neurological disorders are associated with diminished sexual arousal, but proper counseling and rehabilitation, especially in patients with brain injury, may lead to an improvement in libido and other sexual dysfunctions. Thus, although desire disorders in neurological disease may be multifactorial in pathogenesis, treating the primary CNS disease, by itself or in conjunction with other treatment modalities, may well help to recovery sexual libido. Male sexual dysfunction associated with insufficient androgen levels can be treated by testosterone replacement therapy (i.e. intramuscular injection of long-acting testosterone esters in oil) [23-24]. Among the various centrally acting agents, administration of dopaminoagonists (apomorphine, bromocriptine, pergolide and cabergoline) and the new antidepressant drug bupropion has been associated with increased libido. Psychosexual approach may be useful in many cases, even if desire disorders have a substantially poorer response than other forms of sexual dysfunction.

B. Hypersexuality

Increased sexual desire that as to be treated is rare and it is more often reported in neurodegenerative disorders or after brain injury involving specific neural pathways. In some circumstances, androgen antagonists (i.e. cyproterone acetate, medroxyprogesterone acetate) may be effective; in severe cases neuroleptics should be used.

Pelvic Floor Rehabilitation

Erectile dysfunction is defined as the persistent failure to achieve and sustain erections of sufficient rigidity for penetration during sexual intercourse. The role of the perineal muscles in the erectile mechanism is still under debate. Perineal musculature is composed of two kinds of muscle fibers [25]. Slow contraction fibers (Type I) are responsible for the muscle tone and

organ support while fast contracting fibers (type II), localized mainly at the periurethral sphincter level, and are responsible together with the aponeurotic elements of the urethral closure during the abdominal pressure increase. Aim of the perineal rehabilitation is to tones up and to strength both muscle fibers; the slow fibers with smooth and long contractions and the fast fibers with stronger and faster contractions. The final effect of the reinforcement treatment is to increase the motor units, improve the excitation frequency, increase the muscle mass.

Superficial pelvic floor muscles, which are active during erection enhancing rigidity, are located besides the ischiocavernosus and bulbocavernosus muscles. The bulbocavernosus muscle has three functions: it is responsible for preventing blood from escaping during an erection by exerting pressure on the deep dorsal vein; it is active and pumps during ejaculation; and it empties the bulbar urethra by reflex action after micturition (26). Thus, pelvic floor muscle exercises should be considered as a first-line approach for men seeking long-term resolution of erectile dysfunction without acute pharmacological and surgical interventions. Perineal conservative treatment includes different types of perineal rehabilitation, i.e. the pelvic floor muscle training (PFMT), the biofeedback (BFB), the functional electric stimulation (FES), and the programs of perineal re-education. Direct interventions prescribed by physical therapists include the following elements: coordination of care, communication and documentation, patient education and direct intervention i.e. treatment of pelvic floor muscle disorders. The primary intervention prescribed by physical therapists has always been therapeutic exercises including core strengthening of abdominal muscles, postural and pelvic floor muscles [27]. Breathing and relaxation exercises are typical key components of patient rehabilitation. Relaxation involves the quieting of the autonomic nervous system and includes visualization [28], soft tissue mobilization, heat modalities and positioning. Scar management (abdominal or perineal) includes soft tissue mobilization, application of heat or cold, and therapeutic ultrasound. Manual therapy techniques include myofascial release, trigger point release, soft tissue mobilization and massage [29]. The exercise program starts with the supine position, followed by exercises in the side position, standing position, and crawling position. In these positions the duration of contractions of the pelvic floor muscles varies from 3 to 30 seconds. The frequency of contractions varies from 10 to 30 times, equally parted between quick and sustained contractions. Methods of strengthening may include electrical stimulation, muscle re-education using biofeedback techniques or instruction.

Biofeedback involves the use of external or internal sensors that record levels of muscle activity, which are displayed on a computer while the patient do exercises. This visual technique can provide motivational support as it increases the awareness of correct muscle contractions in various positions. Pelvic floor biofeedback therapy is a treatment intended to help patients learn strengthening and relaxing their pelvic muscles. It uses electronic and mechanical instruments to accurately measure the action of pelvic floor muscle, and provides ‘feedback’ information to the patient so to learn how better use the pelvic muscles. Biofeedback uses computer graphs or lights as a teaching tool to help patient identify and learn the correct muscle control and better locate the pelvic muscles by changing the graph of light when he squeezes (tighten) the right muscle. A sensor is placed in the rectum to sense the contraction of the pelvic muscles.

The system can also deliver a painless electrical stimulation to the pelvic muscles which causes their contraction. The patient both workout and learn the right sensation of pelvic

muscle contraction through this stimulation. Muscle strength is assessed also using an anal manometer; each participant is positioned supine with a view of the computer screen for feedback. The air-filled, sheathed and lubricated anal probe, with a diameter of 1 cm, is inserted into the anal canal as far as the probe external position marker (to a depth of 4 cm) in order to approximate to the puborectalis muscle. Patients are instructed to voluntarily tighten and lift the pelvic floor muscles as strongly as possible as if preventing the flow of urine, and to hold this contraction for 10 seconds. A scrotal lift and penile retraction is confirmed to ascertain that the pelvic floor muscles are contracting correctly. The maximum anal pressure reading achieves from the best of three pelvic floor muscle contractions (maximum anal pressure) and the lowest pressure obtained while attempting to maintain a 10-second hold (anal hold pressure) is recorded in cmH2O. A resting time of 10 seconds is often given between each contraction. Biofeedback treatment is accomplished also trough the use of an anal probe attached to a portable electromyography. The activity registered from the pelvic floor muscles and the sphincter is collected by electromyography using surface electrodes. Surface electrodes are placed at both sides of the anus, after drying the area and localized the sphincter of the anus: the two active electrodes are placed laterally to the anus; the reference electrode is placed in a neutral area, usually an arm or a leg.

Electrical stimulation is used to improve awareness of the muscles of the pelvic region and to assist the patient in contracting the ischiocavernosus and bulbocavernosus muscles (30). A symmetric biphasic low-frequency current is used with either an anal plug or superficial electrodes on the centrum tendineum. Pulse frequency is 50 Hz, and pulse duration is 200 microseconds. Each burst of electrical stimulation lasts 6 seconds, with a 12-second rest between bursts. The electrical stimulation lasts for 15 minutes, with an intensity of stimulation that achieved a muscle contraction within the patient's pain limit. As a rule, an anal plug is used for feedback as well as for stimulation. As soon as the patient is able to voluntarily contract the appropriate muscle, he is asked to repeat the contractions daily. Each patient has to perform 40 short and 50 long-lasting contractions in a prone, sitting, or standing position. Moreover, patients are asked to do 30 contractions in the morning, 30 contractions in the afternoon, and 30 contractions in the evening.

Sacral Neuromodulation

Neuromodulation by means of sacral roots electric stimulation with therapeutic purpose is based on different action mechanism: the central one by efferent nerves (in order to abolish bladder instability by external sphincter contraction); and the peripheral one by building an electric field which stimulates the afferents fibers (myelinated type A-delta and A-beta somatic) transmitting sensorial impulse form the corresponding metamers to the sacral roots S2-S4 [31-32]

As therapeutically technique, sacral neuromodulation has founded its place in chronic urination dysfunctional treatment after failure of several treatments. According to FDA, indications are: urgency urinary incontinence because of overactive bladder, associate to fecal incontinence or urethral overactivity; bladder outlet dysfunction and urgency frequency syndrome or not; chronic pelvic pain. Clinically it is also used for enuresis, detrusor-sphincter dyssynergia and interstitial cystitis.

Before Neuromodulation can be applied, patient should be accurately evaluated in order to evidentiate his ability to collaborate in fulfilling urinary diary and Quolity of Life questionnaire. The urodynamics diagnosis results fundamental to determine the type of mictional alteration.

The phases of sacral neuromodulation are the following:

- *Sacral Root evaluation*: This first phase consist of the placement of an electrode in the sacral foramen S3, which would be connected to a external stimulus generator for 5 to 7 days with the objective of evaluating the integrity of the motor and sensorial somatic fibers (the motor answer is the pelvic floor contraction; the sensitive is the paresthesia in the perineum and the external genitalia).
- *Subchronic Phase*: The second phase determines the therapeutic effect of the stimulation by means of mictional diary in the patient, which must be over 50% than the initial symptoms.
- *Definitive implantation*: It consists of the placement of a four definitive electrodes of stimulation within different sides. Every single electrode is surgically placed under general anesthesia with long life muscle relaxants in order to reproduce the answer achieved in the evaluation of the sacral roots. Thereafter they are connected subcutaneously to an impulse generator placed in the external superior quadrant of the gluteus muscle or in the anterior abdominal region. Nevertheless, the placement of a percutaneous definitive electrode connected with a subcutaneous generator under local anesthesia has been recently developed, in order to reduce patients' surgical injuries and X-ray exposure.

Table 2. EFNS recommendations for treatment option in neurosexology

	Treatment options
Permission	Counselling to open the mind of the patients to the existence of sexual disabilities
Limited information	Giving the patients proper information about sexual issues in his particular type of disorder/injury
Specific suggestions	Practical information about position and stimulation techniques (vibrators) and technical aids and devices (vacuum extractor devices) should be given
Intensive therapy	Using specific medical as well as surgical, treatment available, for the different types of problems (i.e. i-PDE).
Assisted fertilization (*spinal cord injuries only*)	Semen can be retrieved by the use of penile vibratory stimulation (PVS) or Rectal probe electroejaculation.

Conclusion

Sexual disabilities such as loss of desire, erectile dysfunction and disturbance in ejaculation and orgasm are very common among patients with neurological disorders. Thus, all neurological patients should have the opportunity of sexual counselling. A careful case history should be taken, neurological examination should include the sacral segments and neurophysiological test, in addition to other indicated investigations, should be considered in patients seeking medical advice because of a sexual disability.

EFNS treatment options in patients affected by neurogenic sexual dysfunctions are shown in table 2.

References

[1] Campbell HE. Clinical monograph for drug formulary review: erectile dysfunction agents. *J. Mana.g Care Pharm.* 2005;11:151-71.

[2] Francis SH, Corbin JD. Sildenafil: efficacy, safety, tolerability and mechanism of action in treating erectile dysfunction. *Expert Opin. Drug Metab. Toxicol*. 2005;1:283-93

[3] Hatzimouratidis K, Hatzichristou DG. Looking to the future for erectile dysfunction therapies. *Drugs*. 2008;68:231-50.

[4] Lombardi G, Macchiarella A, Del Popolo G. Efficacy and Safety of Tadalafil for Erectile Dysfunction in Patients with Multiple Sclerosis. *J. Sex Med*. 2010 Apr 1.

[5] Lombardi G, Macchiarella A, Cecconi F, Del Popolo G. Ten-year follow-up of sildenafil use in spinal cord-injured patients with erectile dysfunction. *J. Sex Med*. 2009;6:3449-57

[6] Shindel AW. 2009 update on phosphodiesterase type 5 inhibitor therapy part 2: updates on optimal utilization for sexual concerns and rare toxicities in this class. *J. Sex Med*. 2009; 6:2352-64

[7] Shindel AW. 2009 update on phosphodiesterase type 5 inhibitor therapy part 1: Recent studies on routine dosing for penile rehabilitation, lower urinary tract symptoms, and other indications (CME). *J. Sex Med*. 2009;6:1794-808

[8] Goldstein I.Oral phentolamine: an alpha-1, alpha-2 adrenergic antagonist for the treatment of erectile dysfunction. *Int. J. Impot. Res*. 2000;12 Suppl 1:S75-80.

[9] Andersson KE. Pharmacology of penile erection. *Pharmacol. Rev.* 2001;53:417-50.

[10] Kandeel FR, Koussa VK, Swerdloff RS. Male sexual function and its disorders: physiology, pathophysiology, clinical investigation, and treatment. *Endocr. Rev.* 2001;22(3):342-88

[11] Feifer A, Carrier S. Pharmacotherapy for erectile dysfunction. Expert Opin Investig Drugs. 2008;17(5):679-90.

[12] van Ahlen H, Piechota HJ, Kias HJ, Brennemann W, Klingmüller D. Opiate antagonists in erectile dysfunction: a possible new treatment option? Results of a pilot study with naltrexone. *Eur. Urol*. 1995;28:246-50

[13] Tamler R, Mechanick JI Dietary supplements and nutraceuticals in the management of andrologic disorders. *Endocrinol. Metab. Clin. North Am.* 2007;36:533-52

[14] Eardley I, Donatucci C, Corbin J, El-Meliegy A, Hatzimouratidis K, McVary K, Munarriz R, Lee SW. Pharmacotherapy for erectile dysfunction. *J. Sex Med.* 2010;7:524-40.
[15] Lundberg Po, Ertekin C, Ghezzi A, Swash M and Vodusek D. Neurosexology. *Eur. J. Neurol.* 2001, 8 (supp 3): 2-24.
[16] Linet OI, Ogrinc FG. Efficacy and safety of intracavernosal alprostadil in men with erectile dysfunction. The Alprostadil Study Group. *N. Engl. J. Med*. 1996;334:873-7
[17] Dinsmore WW, Wyllie MG. Vasoactive intestinal polypeptide/phentolamine for intracavernosal injection in erectile dysfunction. *BJU Int*. 2008;102:933-7.
[18] Giuliano F, Hellstrom WJ. The pharmacological treatment of premature ejaculation. *BJU Int*. 2008;102:668-75
[19] Giuliano F, Clément P. Serotonin and premature ejaculation: from physiology to patient management. *Eur. Urol*. 2006;50:454-66
[20] McMahon CG. Dapoxetine for premature ejaculation. *Expert Opin. Pharmacother*. 2010;11:1741-52.
[21] Soler JM, Previnaire JG, Plante P, Denys P, Chartier-Kastler E. Midodrine improves ejaculation in spinal cord injured men. *J. Urol.* 2007;178:2082-6
[22] Calabrò RS, Marra A, Quattrini F, Gervasi G, Levita A, Bramanti P. Central Neuropathic Pain: An Unusual Case of Painful Ejaculation Responding to Topiramate. *J. Sex Med*. 2010 May 26.
[23] Hatzimouratidis K, Hatzichristou D. Testosterone and erectile function: an unresolved enigma. *Eur. Urol.* 2007;52:26-8.
[24] Traish AM, Goldstein I, Kim NN. Testosterone and erectile function: from basic research to a new clinical paradigm for managing men with androgen insufficiency and erectile dysfunction. *Eur. Urol.* 2007;52:54-70
[25] Serra L. Fisioterapia perineal. En: Tratado de reeducación urogineproctológica. Salinas J, Rapáriz M. 263-292. Gráficas Santer SL. Madrid., 1997.
[26] Dorey G, Speakman M, Feneley R, Swinkels A, Dunn C, Ewings P. Pelvic floor exercises for treating post-micturium dribble in men with erectile dysfunction: a randomized controlled trial. *Urol. Nurs.* 2004;54:819-25.
[27] Kegel AH. Progressive resistance exercise in the functional restoration of the perineal muscles. *Am. J. Obstet. Gynecol.* 1948;56:238-49.
[28] Burgio KL. Influence of behavior modification on overactive bladder. Urol 2002, 60; 72-7.
[29] Weis JM. Pelvic floor myofascial trigger points. *J.Urol.* 2001;166: 2226-31.
[30] Bok K, Talseth T, Holme I. Single blind, randomized controlled trial of pelvic floor exercises, electrical stimulation, vaginal cones, and no treatment in the management of genuine stress incontinence in women. *Brit. Med. J.* 1999; 318: 487-93.
[31] Leng WW, Chancellor MB. How sacral nerve stimulation neuromodulation works. *Urol. Clin. North Am.* 2005;32:11-8.
[32] Aboseif SR, Kim DH, Rieder JM, Rhee EY, Menefee SA, Kaswick JR, Ree MH.Sacral neuromodulation: cost considerations and clinical benefits. *Urology*. 2007;70:1069-73; discussion 1073-4

Authors' Affiliations

Editor/author

Rocco Salvatore Calabrò, MD (Neurologist and Sexologist), PhD (Psychiatric Sciences),
IRCCS Centro Neurolesi "Bonino-Pulejo", Messina, Italy.

Co-authors:

- ***Annalisa Baglieri***, Psychologist, IRCCS Centro Neurolesi "Bonino-Pulejo", Messina, Italy
- ***Placido Bramanti***, MD, Scientific Director, IRCCS Centro Neurolesi "Bonino-Pulejo", Messina, Italy
- ***Francesco Cordici***, MD, PhD, IRCCS Centro Neurolesi "Bonino-Pulejo", Messina, Italy
- ***D'Aleo Giangaetano***, MD, IRCCS Centro Neurolesi "Bonino-Pulejo", Messina, Italy
- ***Lorenzo De Santi***, MD, IRCCS Centro Neurolesi "Bonino-Pulejo", Messina, Italy
- ***Giuseppina Digangi***, Psychologist and Psychotherapist, IRCCS Centro Neurolesi "Bonino-Pulejo", Messina, Italy
- ***Paolo Di Bella***, MD, IRCCS Centro Neurolesi "Bonino-Pulejo",Messina, Italy
- ***Anna Furnari***, MD, IRCCS Centro Neurolesi "Bonino-Pulejo", Messina, Italy
- ***Giuseppe Gervasi***, MD, IRCCS Centro Neurolesi "Bonino-Pulejo", Messina, Italy
- ***Jacopo Grisolaghi***, Psychologist, Dipartimento di Psicologia, Università di Firenze, Florence, Italy.
- ***Domenico Italiano***, MD, IRCCS Centro Neurolesi "Bonino-Pulejo", Messina, Italy
- ***Antonino Levita***, MD, IRCCS Centro Neurolesi "Bonino-Pulejo", Messina, Italy
- ***Silvia Marino***, MD, PhD, IRCCS Centro Neurolesi "Bonino-Pulejo", Messina, Italy
- ***Adriana Magaudda***, MD, Epilepsy Center, Policlinico Universitario, Messina, Italy.
- ***Nunzio Muscarà***, IRCCS Centro Neurolesi "Bonino-Pulejo", Messina, Italy
- ***Concetta Pastura***, MD, IRCCS Centro Neurolesi "Bonino-Pulejo", Messina, Italy
- ***Fabrizio Quattrini***, Psychosexologist, Università de L'Aquila, L'Aquila, Italy
- ***Carmela Rifici***, MD, IRCCS Centro Neurolesi "Bonino-Pulejo", Messina, Italy
- ***Edoardo Sessa***, MD, IRCCS Centro Neurolesi "Bonino-Pulejo", Messina, Italy

Index

A

B

C

D

E

F

G

H

I

J

K

L

M

N

O

P

Q

R

S

T

U

V

W

X

Y

Z