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Epidemiology and pathophysiology of male sexual dysfunction

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Male sexual dysfunction (MSD) is a common disorder associated with a wide range of physical and psychological conditions. Erectile dysfunction, the most commonly studied aspect of MSD, is common and increases with age and with certain comorbid conditions. The pathophysiology of ED and other forms of MSD can be traced to a variety of etiologies, including vascular, hormonal, psychiatric, iatrogenic and potentially neurobiological causes.
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Introduction

Male sexual dysfunction (MSD) is a common disorder that appears to be a consequence of a wide range of physical and psychological conditions. In the medical community, much of the current focus is on end-organ function of the penis, which highlights the currently available treatment options, including phosphodiesterase-5 (PDE-5) inhibitors and alprostadil.[1] Hypogonadism and the relative contributions of testosterone to the male sexual cycle of desire and arousal have also been extensively studied. While these investigations have greatly enhanced our understanding of both normal and abnormal sexual response, much work remains to be done, including investigations of the role of the central nervous system (CNS) in sexual response. Broadening our understanding of the male sexual response may open up new opportunities for appropriate intervention.

Definitions

The Second International Consultation on Sexual Medicine defined disorders of sexual function in men include erectile dysfunction (ED), orgasm/ejaculation disorders, priapism and Peyronie's disease.[2] These definitions perhaps overemphasize the end-organ process, but highlight the relatively straightforward approach to management of MSD; that is to say, assuring that the penis works to the patient's satisfaction. ED is further classified by the etiology of the dysfunction such as vasculogenic, psychogenic and neurogenic ED; although in many cases the etiology is considered mixed.

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Epidemiology of MSD

The Massachusetts Male Aging Study (MMAS) provided data on the prevalence and incidence of ED in a population of US men. The MMAS was a cross-sectional, population-based multidisciplinary survey of health in normally aging men (aged 40–70 years) conducted from 1986 to 1989.[3] The MMAS continues to be a rich resource for ongoing research into correlates of male sexual dysfunction.

The original report from the MMAS data divided men with self-reported ED into three broad categories of severity: minimal, moderate and complete. According to this classification scheme, 51% of respondents reported at least some ED, with prevalence of 'complete' ED increasing threefold from the youngest age group to the oldest. ED was also found to be associated with a variety of chronic conditions and their treatments, including heart disease, hypertension and diabetes; cigarette smoking among men with heart disease and hypertension was also associated with a higher risk of any ED. ED was also associated with psychological conditions of anger and depression. Higher testosterone (dehydroepiandrosterone), higher HDL cholesterol and a 'dominant personality' index were all inversely correlated with ED.

Men enrolled in the MMAS were followed longitudinally with results published in 2000 based on a mean of 8.8 years of follow-up.[4] Not unexpectedly, the annual incidence rate of ED increased with each decade of age to a high of 46.4 cases per 1000 man-years (Table 1). The age-adjusted risk

Table 1 Annual incidence rate of ED in MMAS

Age group (years)	*No. of incident erectile dysfunction cases*	*Man-years*	*Incidence per 1000 (95% CI)*
40–49	39	3154	12.4 (9.0–16.9)
50–59	83	2749	29.8 (24.0–37.0)
60–69	72	1572	46.4 (36.9–58.4)

Abbreviations: ED, erectile dysfunction; MMAS, Massachusetts Male Aging Study.
Men initially enrolled in the survey were followed for a mean of 8.8 years.[4]

of ED was higher for men with lower education, diabetes, heart disease and hypertension. Population projections for men aged 40–69 years suggested that more than 600 000 new cases of ED could be expected annually in the United States among white men. This longitudinal analysis was one of the first to recognize the impact of income and/or education on the risk for ED, with ED perhaps being a biomarker for the overall health decrements associated with lower socioeconomic status.

One of the primary criticisms of the MMAS database was that the population studied was not demographically diverse, and therefore results may not be able to be extrapolated beyond white men. One of the primary epidemiological studies to address this issue was the National Health and Social Life Survey, a nationwide probability sample of adults (both men and women) aged 18–59 years.[5] The primary outcome measures of this survey of 1749 women and 1410 men were the risk of experiencing a sexual dysfunction and other concomitant medical outcomes. Male respondents were asked to further define their sexual dysfunction into categories that included lack of interest in sex, inability to achieve orgasm, climaxing too early, lack of pleasure in sex, anxiety about performance and ability to achieve or sustain an erection.

Consistent with the MMAS, the National Health and Social Life Survey found that the oldest cohort (ages 50–59 years) was three times as likely to experience ED and lack of sexual desire as the youngest cohort (ages 18–29 years). Approximately 9% of the cohort reported difficulties in achieving orgasm, which was not age dependent. Premature ejaculation was reported by approximately 30% of the respondents, again with no clear age relationship. Less than 10% of the cohort reported that sex was not pleasurable to them, and about 17% reported that they had anxiety about their sexual performance. Not surprisingly, physical health decrements, and emotional and stress-related issues were associated with a higher risk of sexual dysfunction. Importantly, the National Health and Social Life Survey also confirmed a relationship between abusive childhood sexual encounters and long-term sexual dysfunction in both men and women.

The National Social Life, Health, and Aging Project (NSHAP) was designed to understand the sexual norms of older Americans (from 57 to 85 years).[6] ED was the most frequently reported sexual dysfunction among men (37%), and 90% of those with ED reported that they were bothered by it. In addition, 28% reported a lack of interest in sex, with 65% stating that they were bothered by the symptom. Climaxing too quickly (28% prevalence; 71% bother), performance anxiety (27% prevalence; 75% bother) and inability to climax (20% prevalence; 73% bother) were also commonly reported. Almost half of all respondents reported at least one bothersome symptom, and one-third had at least two such symptoms.

It is likely that some readers of this article participated in the Health Professionals Follow-up Study (HPFS), a cohort of male dentists, optometrists, osteopaths, podiatrists, pharmacists and veterinarians in the United States who responded to a mailed questionnaire in 1986. Every 2 years, an additional survey is distributed, and in 2000, 43 235 participants provided input into the topic of sexual dysfunction.[7] Excluding those who had a diagnosis of prostate cancer, participants were asked to rate their ability to have and maintain an erection suitable for intercourse, without treatment (for example, use of PDE-5 inhibitors). Responses were tabulated on a five-point Likert scale from very poor to very good.

Among this cohort of health-care professionals over the age of 50 years, the age-standardized prevalence of ED in the prior 3 months was reported as being 33%. Unsurprisingly, age-related increases in risk of ED were noted, and good health was associated with a reduced risk for ED. Increasing risk for ED was noted in a continuum by age and with the presence of chronic disease and risk factors for ED, defined in this survey as antidepressant use, consumption of more than two alcoholic drinks per day, smoking, a body mass index $\geqslant 25\,kg\,m^{-2}$, exercise <21.5 metabolic equivalents per week or television viewing >8.5 h a week (Figure 1).

In addition to erectile function, the HPFS noted an age-dependent decrease in sexual desire. Only 2% of respondents under age 59 years reported 'very poor' sexual desire, compared with 24% of those ages 80 years and over. Older respondents were also more likely by age decile to report sexual functioning as a problem. There was a similar age-related relationship with self-reported overall sexual functioning. Whether reduced desire is a cause, consequence or corollary of ED was not explored in this analysis.

Good health practices were associated with reduced risk of ED in the HPFS. For example, regular exercise equivalent to running 3 h a week was associated with a 30% reduced risk of ED when

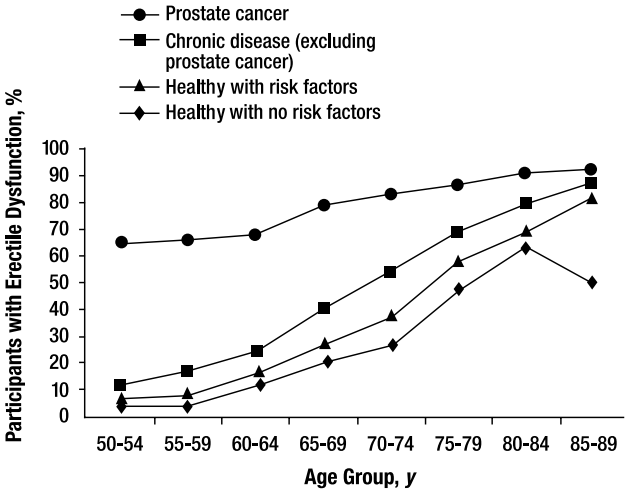


Figure 1 Association of erectile dysfunction (ED) by age category and presence of risk factors (for example, hypertension, high cholesterol, smoking and body mass index $\geqslant 25\,kg\,m^{-2}$) among participants in the Health Professionals Follow-up Study (HPFS). From Bacon CG *et al.*[7] with permission from Annals of Internal Medicine.

compared with those getting little or no exercise. Similarly, both moderate alcohol consumption and being a nonsmoker were inversely correlated with ED.

According to the Olmsted County Study of Urinary Symptoms and Health Status Among Men, age-related reduction in sexual functioning is also associated with worry over sexual functioning, concern over worsening performance over time, extreme dissatisfaction with sexual performance and absent sexual drive.[8] This survey of more than 2100 men aged 40–79 years suggested that sexual dissatisfaction was significantly associated with ED, decreased libido and the interaction between ED and libido, but not age. In logistic regression analysis, age-related increases in sexual dissatisfaction were accounted for primarily by the age-related increase in ED, decreased libido and the interaction between ED and decreased libido. When men aged 70–79 years were compared with those aged 40–49 years, older men reported that they were more worried about sexual function (46.6 vs 24.9%), experienced worsened performance compared with a year ago (30.1 vs 10.4%), expressed extreme dissatisfaction with sexual performance (10.7 vs 1.7%), had absent sexual drive (25.9 vs 0.6%) and reported complete ED when sexually stimulated (27.4 vs 0.3%).

Hypoactive sexual desire disorder is characterized by reduced sexual fantasies and desire for sexual activity. Like other sexual disorders, hypoactive sexual desire disorder does not rise to the level of a condition deserving medical intervention unless the patient is distressed by it.[9] In community surveys, 1-year prevalence estimates for hypoactive sexual desire disorder range from 7 to 16% of the population, with age-related increases up to 26% among men over the age of 75 years.[10]

Pathophysiology of male sexual dysfunction

The evolution of our understanding of the causes and mechanisms of MSD has largely followed the discovery of treatment options that impact one or more pathways. Prior to the advent of pharmacologic solutions for ED, it was assumed that the majority of ED was psychologically based. The advent of prostaglandins and then PDE-5 inhibitors led the way to new understandings of the vasculogenic mechanisms of ED. Research into testosterone supplementation and hypersupplementation provided key insights into the role of the hypothalamic–pituitary axis into sexual function. Additionally, new insights into psychiatric conditions and their treatments have also helped inform us about the role of various neurotransmitter systems in normal and abnormal sexual function. What is clear from this research is that the biological, neurobiological and psychological correlates of male sexuality are much more nuanced than a single, simple 'on–off' switch.

A wide range of general medical disorders and their treatments result in a loss of sexual motivation and other aspects of the sexual response cycle.[11] Some conditions and/or their treatments (for example, depression) interfere with sexual desire; others indirectly interfere with sexual response because of issues such as pain, etc. Cardiovascular conditions, neurodegenerative conditions and endocrinologic conditions are strongly associated with reduced sexual desire or arousal. In men, many of these same conditions also affect erectile function.

Endothelial dysfunction and ED

Endothelial dysfunction refers to decreases in endothelium-dependent smooth muscle relaxation caused by a loss of or increased destruction of nitric oxide (NO) activity. The NO pathway is a critical component of smooth muscle tone, and endothelial NO synthesis is a crucial early step in the process.[12]

The consequences of endothelial dysfunction can be seen in the ability of the penile vasculature to respond to sexual signals. The now-classically understood cascade of events leading to erection begins with NO production in the endothelium and elsewhere, diffusing to the smooth muscle cells of the penile arteries. NO stimulates guanylate cyclase which then converts guanosine triphosphate (GTP) to cyclic guanosine monophosphate (cGMP), inducing a substantial increase in intracellular cGMP, causing smooth muscle relaxation. PDE-5 breaks down cGMP, and provides the basis for the mechanism of action of sildenafil and the other PDE-5 inhibitors[1] (Figure 2). It is unknown whether interventions earlier in the NO cascade might

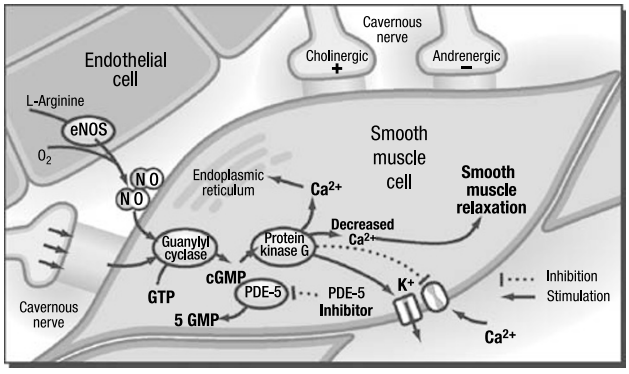
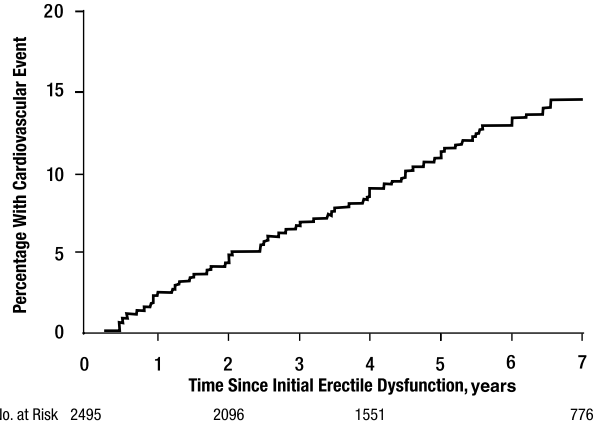


Figure 2 NO pathway of erectile function. NO derived from the endothelium or cavernosal nerves signals guanylate cyclase which then converts guanosine triphosphate (GTP) to cyclic guanosine monophosphate (cGMP), inducing a substantial increase in intracellular cGMP, causing smooth muscle relaxation via sequestration of intracellular calcium (Ca^{++}) in the endoplasmic reticulum and inhibition of Ca^{++} ion channels. PDE-5 breaks down cGMP. Adapted from Lue T.[1]



At risk, $n = 2495$; number of cardiovascular events, 255; 5-year estimate of cardiovascular events, 11%

Figure 3 Time to cardiovascular event from first report of erectile dysfunction (ED) among men enrolled in the Prostate Cancer Prevention Trial. From Thompson IM *et al.*[14] with permission from *JAMA*, 2005, **294**: 2996–3002.

provide additional or different benefits for patients with ED caused by endothelial dysfunction.

We now know that a wide range of chronic conditions have the potential to derange the endothelial structure and function, including atherosclerosis, hypertension, hypercholesterolemia, diabetes mellitus and damage caused by cigarette smoking. Not surprisingly then, the association of ED with these risk factors is strong, and in some instances, almost pathognomonic. The Second Princeton Consensus Conference recently concluded that ED is a warning sign of silent vascular disease and that a man with ED without cardiac symptoms should nonetheless be considered a cardiac (or vascular) patient until proven otherwise.[13] This consensus is supported by data from the Prostate Cancer Prevention Trial, which found that men with ED at study entry had almost double the risk of a subsequent cardiac event than those without ED.[14] There was a highly correlated relationship between the duration of the subjects' ED and a subsequent cardiac event (Figure 3).

Hypertension is the most common primary diagnosis in the United States, affecting about 20–25% of all adults older than the age of 45–50 years, with ED being apparent in approximately 30% of male hypertension patients.[15] The degree of erectile impairment is directly correlated with the severity and duration of hypertension. A recent report found no difference in the prevalence of ED among hypertensive and pre-hypertensive men aged 25–40 years compared with normotensive controls, so the damage caused by hypertension may take years to become evident.[16]

Diabetes mellitus is commonly associated with ED. In the National Health and Nutrition Examination Survey (NHANES) database, the crude prevalence of ED was 51.3% among men with diabetes.[17] The pathophysiology of diabetes-related ED is likely tightly intertwined with the cardiovascular effects of diabetes; as well as reductions in vascular endothelial growth factor expression and signaling, selective degradation of neuronal NO production, activation of the RhoA/Rho kinase pathway and increased levels of erythrocyte aldose reductase.[18–21] ED among men with diabetes is often more refractory to treatment than ED from other etiologies.

Atherosclerosis also contributes to endothelial damage and, along with alterations in the neurogenic pathway, may play a role in ED.[22] Studies of men with elevated cholesterol and ED show impairment in endothelium-dependent smooth muscle relaxation and diminished endothelial nitric oxide synthase activity in the penis.[12] Animal models of hypercholesterolemia show a reduction in endothelial and cavernous smooth muscle cells with loss of intercellular contacts in the corpus cavernosum sinusoids, as well as a reduction of input from myelinated and non-myelinated nerves of the penis.[22,23]

A number of groups have attempted to characterize the link between ED and a diagnosis of metabolic syndrome—the combination of hypertension, dyslipidemia, glucose intolerance and insulin resistance. Of interest is whether this constellation of syndromes is independently associated with a synergistic risk of ED, or whether the component features of metabolic syndrome are merely additive in nature. An Italian study of 100 men with metabolic syndrome showed a straight-line relationship between the prevalence of ED and increases in C-reactive protein levels, endothelial dysfunction and number of components of the metabolic syndrome.[24]

In the urology community, the comorbid incidence of lower urinary tract symptoms and ED is

well established.[25] The pathophysiologic relationship between the two conditions is less well understood. Both conditions are associated with reduced levels of NO synthesis. In addition, the presence of α-adrenergic receptors in the smooth muscle of both the prostate and corpus cavernosum has been proposed as a potential common source of dysfunction and a common target of treatment. Of potential concern, however, is the association between ED and use of finasteride (a 5-α-reductase inhibitor) to treat benign prostatic hyperplasia.

Hormonal pathway of sexual dysfunction

Hypogonadism affects a substantial number of men and progressively worsens with age. Low levels of serum testosterone may lead to reduced muscle mass, loss of bone density, anemia, symptoms of depression, loss of libido, ED and diminished energy.[26] Hypogonadism is estimated to affect 20% of men 65 years and older (Feldman *et al.*[3]) and up to 92% of men older than 80 years.[27] Even among men not diagnosed with overt hypogonadism, both total and free testosterone decline in an age-dependent manner.

However, the relationship between hypogonadism and ED is less clear. Even among men who are surgically or pharmacologically castrated, erectile capacity may not be totally lost. Erectile response to visual erotic stimuli appears to be relatively independent of androgen status. In addition, physiologic response to watching erotic videos among eugonadal men did not include secretion of higher levels of testosterone or luteinizing hormone.[28] Epidemiologic studies generally have not found clear associations between serum testosterone levels and ED.[29] A recent analysis of the MMAS population found that reduced testosterone levels were associated with a decrease in risk of ED only in men with increased luteinizing hormone levels.[30] After adjusting for potential confounding factors, no association was found between ED and levels of total testosterone, bioavailable testosterone or sex hormone-binding globulin.

The association between low testosterone and sexual interest/libido is more clearly established. In fact, the impact of testosterone replacement therapy may be more important in restoring libido than in improving erectile function. An analysis of multiple clinical trials of testosterone replacement therapy showed that testosterone treatment moderately improved the number of nocturnal erections, sexual thoughts and motivation, number of successful intercourses, scores of erectile function and overall sexual satisfaction among hypogonadal, but not eugonadal men.[31] In hypogonadal men who did not respond to tadalafil alone, a 10-week regimen of transdermal testosterone improved erectile function more than a 4-week regimen of testosterone, implying that testosterone-related remodeling of penile tissues may be occurring.[32]

Table 2 Sexual functions affected by testosterone therapy in hypogonadal men

Sexual functions improved by testosterone
- Sexual desire
- Spontaneous sexual thoughts
- Attentiveness to erotic auditory stimuli
- Frequency of daytime erections
- Duration, magnitude and frequency of nocturnal penile erections
- Overall sexual activity scores
- Volume of ejaculate

No improvement or insufficient evidence
- Erectile response to visual erotic stimulus
- Therapeutic response to selective phosphodiesterase inhibitors
- Orgasms

Adapted from Bhasin *et al.*[34]

The threshold for testosterone deficiency to result in reduced libido may be less than that associated with purely hypogonadal-related ED. In an analysis of 434 men aged 50–86 years, various strata of serum total testosterone concentrations were associated with specific symptoms.[33] Loss of libido occurred with total testosterone <15 nM, while ED was associated with lower testosterone levels (<8 nM).

It has also been shown that hypogonadal men who are provided with testosterone replacement therapy regain spontaneous nocturnal erections but do not regain erectile response to erotic stimuli.[34] While some aspects of sexual function do appear to be improved by replacing testosterone in hypogonadal men, others appear not to be impacted by such treatment (Table 2). In addition, there is little evidence that hypersupplementation of testosterone in eugonadal men has any benefit.

CNS pathway of sexual dysfunction

Research into the role of the CNS in sexual function and dysfunction continues to emerge. This research reveals an interconnected role of the sex steroids and neurotransmitters in the CNS and periphery. Neurotransmitters modulate the secretion of many hormones involved in sexual functional capacity, while at the same time, hormones influence synthesis and storage of central neurotransmitters.[35]

Functional magnetic resonance imaging has begun to elucidate the areas of the brain associated with sexual response, revealing a complex neural circuit involved in sexual arousal.[36] A few areas (anterior cingulate, insula, amygdala, hypothalamus and secondary somatosensory cortices) were specifically correlated with penile erection in healthy

subjects. However, in a study of middle-aged men who did not have either ED or reduced sexual desire, the hypothalamus and thalamus were not activated in response to erotic stimuli, which may help account for the lesser physiological arousal in response to erotic visual stimuli.[37]

Although spinal neurons controlling erection are activated by information from peripheral and supraspinal sources, some supraspinal structures that have a pro-erectile effect may not project directly onto spinal neurons involved in erection. These structures, including the paraventricular nucleus and the medial preoptic area of the hypothalamus, regulate erection by coordinating responses of the body during sexual or pro-sexual activity.[38] A variety of neurotransmitters are released by the spinal network that controls penile erection.

The dopaminergic system appears to be intricately linked to sexual response. An increase in sexual activity is often noted in patients being treated with L-DOPA for Parkinson's disease, and may actually precede improvement of neurological symptoms. Since L-DOPA is always administered with a peripheral decarboxylase inhibitor, the mechanism of action of dopamine on sexual response is necessarily related to its central effects.[39] Treatment of hyperprolactinemia with dopamine agonists often results in rapid improvement of sexual symptoms.[40] In addition, dopamine-blocking agents such as haloperidol and chlorpromazine used for psychotic conditions often result in a reduction in sexual activity. Although this evidence is indirect in nature, it points strongly to a central component of dopamine in promoting the sexual response.

In the CNS, serotonin is primarily an inhibitor of sexual response. Sexual dysfunction has long been observed with the use of selective serotonin reuptake inhibitors for the treatment of depression.[41] These effects were noted in a cross-sectional observational study conducted in more than 1100 primary care clinics in the US, of more than 6200 adult patients receiving antidepressant monotherapy. In this population, the overall prevalence of sexual dysfunction was 37%. Sexual side effects were most prevalent among patients receiving selective serotonin reuptake inhibitors and venflaxine SR compared with non-serotonergic agents such as bupropion. These data appear to confirm the role of serotonin as a centrally acting downregulator of sexual function.

The relationship between mood and sexual interest is also well established. Major depressive disorder has long been recognized as resulting in reduced interest in sex, most likely due to the general anhedonia associated with depression.[42,43] Up to 80% of patients report reduced libido as a symptom of their depression. In a *post hoc* analysis of the MMAS, depressive symptoms, as measured by a score of 16 or greater on the Center for Epidemiological Studies Depression scale, were used as predictors of ED.[44] ED was associated with depressive symptoms after controlling for potential confounders. The relationship between depressive symptoms and ED in middle-aged men was robust and independent of important confounders associated with aging, including demographic, anthropometric and lifestyle factors, health status and use of medications. Panic disorder and post-traumatic stress disorder are also associated with ED. In one cohort of military combat veterans with post-traumatic stress disorder, 85% reported ED, compared with 22% of controls.[45]

In the hypothalamus and associated limbic structures, dopamine and serotonin may modulate testosterone function. Decreased levels of bioavailable testosterone may lead to mood-related symptoms such as dysphoria and diminished libido. Prolactin is another neurohormone that is part of the hypothalamic–testicular–pituitary axis implicated in ED. ED is often the primary complaint among men who are discovered to have hyperprolactinemia.[46] Although rare, the possibility of a prolactinoma should be considered among men for whom other more common causes of ED or loss of libido are absent.

High rates of reduced sexual desire have been reported in patients with head trauma, especially hypothalamic and pituitary damage associated with traumatic brain injuries.[47] Head injuries may be associated with central hypogonadism, as well as reduced release of growth hormone, and/or gonadotropin. Stroke appears to result in similar rates of sexual dysfunction as with head trauma, although sexual disorders are rarely a direct consequence of the stroke. Rather, underlying conditions that lead to stroke (for example, hypertension and diabetes) are also associated with high rates of sexual dysfunction, especially ED.

Melanocortins are a newly described group of small-protein molecules that have both peripheral and central effects.[48] Five melanocortin receptors have been identified in both the CNS and periphery, and are associated with skin coloration, weight and sexual response. The five melanocortin receptors have different binding affinities for the various melanocortin peptides. Sexual behavior is thought to be regulated by the melanocortin 4 receptor, which is also implicated in the control of food intake and energy expenditure.[49] Of interest is the potential interrelationship between appetite and sexual response that may be mediated by the melanocortin 4 receptor. Energy homeostasis and reproductive function may be modulated by the same neurotransmitter systems, such as the role of the satiety hormone leptin on reproductive function. Bremelanotide, a selective melanocortin 4 receptor agonist in clinical development for sexual dysfunction in both men and women will be reviewed elsewhere in this supplement.

Conclusions

Sexual desire and activity are widespread among middle-aged and elderly men and women, and persist into old age.[50] As the population ages, prevalence of ED and other sexual dysfunctions will continue to increase. These sexual dysfunctions may cause patients significant distress and deserve attention and care.

Our understanding of the pathophysiology of MSD in general and ED in particular has been driven by the availability of therapies that impact one or more pathophysiologic pathways. PDE-5 inhibitors have undoubtedly provided benefits to millions of men suffering from ED. Our understanding of the hormonal pathways of sexual function also continues to improve as we gain further understanding of both the central and peripheral roles of hormones on the sexual response cycle.

Other components of the overall male sexual response are just beginning to gain research attention. Ongoing research into alternative pathways of enhancing the male sexual response, including centrally acting agents, holds potential to further break through treatment barriers.

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Disclosure

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