Sexual dysfunction

A C SCHMIDT
MB ChB, MMed (Urol)

Lecturer/Senior Specialist
Department of Urology
University of Stellenbosch
Tygerberg

Sexual dysfunction is not only a distressing condition but often a symptom of serious underlying pathology.

As the causes and mechanisms of male erectile dysfunction (ED) were unravelled, it became more and more obvious that ED is an important marker of underlying physical or psychological pathology. The importance of sexual function as part of quality of life is reflected in the World Health Organisation's definition of health as not merely the absence of disease, but total physical, emotional and social well-being.[1]

Research during the past two decades has uncovered much concerning sexual function. The impact of sexuality on any society is illustrated by the multitude of references to sexuality observed in everyday life. Because male sexual dysfunction is made more obvious by the absence of an erection and societies are usually male dominated, research was initially directed at male sexual dysfunction. The increased awareness of sexuality led to an increase in research on other aspects of sexuality, including female sexual function.

MALE SEXUAL DYSFUNCTION

The National Institutes of Health consensus meeting during 1993 suggested that the negative term impotence be replaced with ED,[2] which is defined as the inability to attain and maintain an erection for satisfactory sexual function. The importance of duration or persistence and degree of erectile failure were highlighted during the First Consultation Meeting on Erectile Function in Paris during July 1999.[3] This allows division of ED into primary (whole life) and secondary (change after being normal) and into partial, moderate or total (degree of erectile dysfunction).

Male sexual dysfunction may be divided into desire or libido disorders, ED, and ejaculatory and orgasmic disorders.

Erectile dysfunction

Epidemiology

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Prevalence and incidence

Spector and Carey published a critical review of the prevalence (existing cases in a population) and the incidence (new cases in a population over a discrete period in time) of sexual dysfunction in 1990.[5] The prevalence of ED varies significantly according to the population studied. The prevalence reported from studies conducted in clinics is usually higher than in population-based studies, depending on the occurrence of risk factors and the mean age of patients. Two large population-based surveys (Massachusetts Male Ageing Study (MMAS) and the National Health and Social Life Study (NHSLS)) have recently been published.[3] According to the MMAS, 52% of males between 40 and 70

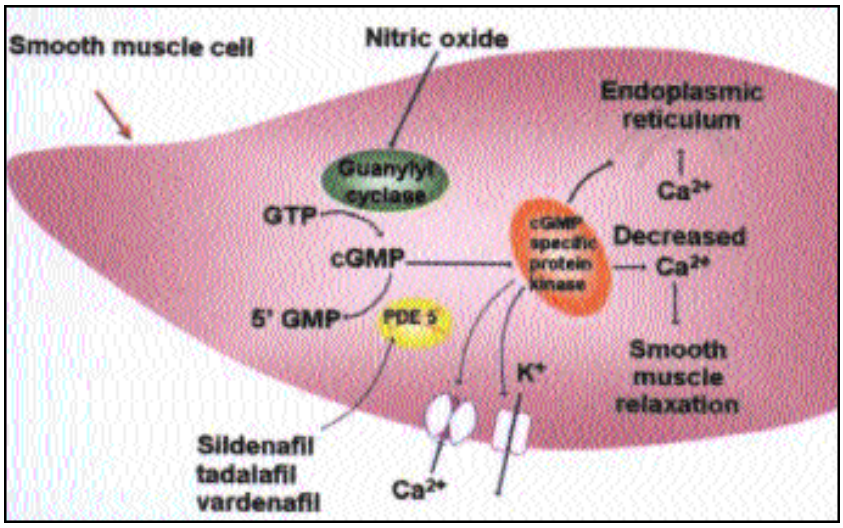

Fig. 1. Mechanism of penile erection.

years of age suffer from ED, with the prevalence of minimal ED unchanged at 17%, moderate ED increased from 17% to 34% and total ED increased from 5% to 15% in the 40 - 70-year age group.

Mechanisms of erection[6] (Fig. 1)

Erection is initiated by 2 separate but closely linked mechanisms namely, the psychogenic and reflexogenic mechanisms. The psychogenic mechanism is initiated by external stimuli to the primitive areas of the brain, the visual, auditory and olfactory areas and relayed to central nuclei located mainly in the ventral hypothalamic and median pre-optic areas. This results in primarily dopaminergic type 2 receptor stimulation. Impulses are then relayed through the brainstem and inter-mediolateral cell column to lower thoracic spinal nuclei. They exit the spinal column via the greater splanchnic outflow to the sympathetic chain and the perivesical plexus. The reflexogenic mechanism is initiated by local stimulation of penile receptors and relayed to the spinal column via afferent nerves to the sacral spinal nerves at S2 - S4 level. It is then relayed via interneurons to anterior motor nuclei, from where efferent nerves from S2 - S4 level complete the reflex arch back to the perivesical plexus. From the perivesical plexus, pre- and post-ganglionic nerves are projected to the pelvic blood vessels and via the cavernous nerves to the smooth muscle of the cavernous bodies and the blood vessels of the penis.

In the smooth muscles of the blood vessels and cavernous bodies of the penis, non-cholenergic non-adrenergic nerves cause the release of the neurotransmitter, nitric oxide (NO), which stimulates guanylyl cyclase (GC). GC stimulates the conversion of guanosine triphosphate (GTP) to cyclic guanosine monophosphate (cGMP), which decreases intracellular calcium and causes smooth-muscle relaxation. Smooth-muscle relaxation causes vasodilatation, an increase of blood inflow, expansion of the cavernous bodies, compression of subtunical venous plexus, trapping of blood and the initiation of erection. Cholinergic nerves also stimulate smooth-muscle relaxation, mainly by inhibition of adrenergic nerves. Adrenergic nerves cause smooth-muscle contraction and inhibition of the erectile response.

Risk factors for erectile dysfunction

ED indicates endothelial dysfunction. The deadly quintet of endothelial dysfunction, diabetes mellitus, hypertension, hyperlipidaemia and obesity, including low serum levels of HDL lipoproteins, arteriosclerosis and peripheral vascular disease are all cardiovascular risk factors that have a high correlation with ED.

Depression and its medical treatment are associated with ED.[7] There are reports indicating that treatment of ED sometimes alleviates the symptoms of depression. Depression carries a serious suicide risk (up to 15%) and patients often stop antidepressive therapy because of the ED associated with antidepressive therapy.

Risk factors for ED may be classified into 3 groups — health and lifestyle, social status and sexual experience. Deterioration in health, urinary tract symptoms, emotional and stress-related problems, poor economic position and liberal attitudes towards sex are associated with premature ejaculation and ED. Multiple partners and masturbation do not increase the risk of sexual dysfunction, but men who sexually assault women, men with same-sex experience, and male victims of adult-child or forced sexual contact are more likely to experience ED and premature ejaculation.

There are several links between ED and lower urinary tract symptoms (LUTS). Radical pelvic surgery, especially radical prostatectomy, is frequently associated with ED.

Androgens influence the growth and development of the male reproductive system and secondary sexual characteristics. The effect of androgen on libido and sexual behaviour is well established, but

the effects on the erectile mechanism remain unclear. According to the MMAS, testosterone (total, free or albumin bound, or dihydrotestosterone) was not statistically correlated with ED. No correlation was found with any of 17 hormones measured. This included FSH, LH, prolactin, androstenedione, androstanediol, and oestrogen.The exception was DHEAS, where levels below 0.5 mg/ml were associated with ED.[3]

The use of tobacco is clearly a risk factor for ED. In the MMAS, cigarette smoking exacerbated the risk of ED along with cardiovascular disease and medication.

ED has been reported in at least 50% of diabetics. The pathological effects of diabetes mellitus on tissue, such as small arterial and arteriolar effects, neurological demyelinisation and sinusoidal smooth-muscle deterioration, have been implicated as risk factors. Impaired autonomic nerve-mediated and endothelium-dependent relaxation, with maintenance of autonomic nerve-mediated contraction, has been reported in diabetics.

Chronic neurological disease, such as Parkinson's disease, cardiovascular accident, temporal lobe epilepsy, multiple sclerosis and autonomic neuropathy associated with AIDS, chronic renal failure, and obstructed lung disease are strongly correlated with a high risk for ED.

Medication, especially antipsychotic, antihypertensive and anti-androgenic therapy, is often associated with changes in sexual function.

Evaluation

ED may be classified according to the major aetiological cause, for example psychogenic or organic. Organic aetiologies include vascular, endocrine, neurogenic, penile or urological conditions, systemic disease or medications. ED is often a symptom of underlying pathology, usually of mixed aetiology and may be a threat to health and quality of life. It has a serious impact on couples. After excluding serious and life-threatening medical conditions, for example the 'deadly quartet', depression, prostatic conditions and medications, therapy is indicated according to the couple's expectations. The minimal work-up consists of a thorough history, physical examination, serum glucose, total testosterone, lipid profile and a prostate specific antigen in patients older than 50 years. Other special investigations should be done as indicated by the history and physical examination.

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Treatment modalities

After underlying pathology, such as personal problems, depression, hypertension, diabetes and hyperprolactinaemia has been addressed, further management must be initiated by the couple. Some may request further investigations to establish the cause or need a referral to a specialist (psychologist or sexologist), while others may be satisfied with no further treatment.

Oral therapy has revolutionised the treatment of ED. Peripheral acting medication, phosphodiesterase (PDE) type 5 inhibitors, are considered first-line therapy. There are 3 PDE type 5 inhibitors — sildenafil, vardenafil and tadalafil, which are registered or filed for registration in South Africa. Therapeutic activity has been established for all 3 in extensive clinical studies. The main differences of the PDE type 5 inhibitors are illustrated in the table of their pharmacokinetics (Table I).

Sildenafil and vardenafil have a quicker onset of response that lasts for about 12 - 18 hours, but tadalafil still has a response in 80% of patients after 36 hours. All PDE type 5 inhibitors potentiate the hypotensive effect of organic nitrates and are contraindicated in patients taking organic nitrates in any form. Their use was not associated with an increased risk of myocardial infarction or death in controlled clinical trials. The most common adverse effects were headache, facial flushing, dyspepsia, visual disturbances and myalgia.

Patients with centrally active pathology (psychogenic ED) or mild to moderate ED due to other causes, may be treated with the centrally acting dopaminergic stimulating drugs. Apomorphine, a D_2 receptor agonist, has been registered in South Africa for clinical use. It has been proved to be safe in extensive clinical studies, it may be taken with food and the use of alcohol is not contraindicated. Although apomorphine may have had less therapeutic response than the PDE type 5 inhibitors in clinical trials, it can offer safe and

Table I. PDE5 inhibitors: pharmacokinetics

Parameter (median)	Sildenafil*	Tadalafil†	Vardenafil‡
Bioavailability	**40%**	**nd**	**15%**
C_{max} with food	29%	No change	20%
t_{max} (h)	1	2	1
$t^1/_2$ (h)	3 - 5	17.5	~4

* Viagra (sildenafil) prescribing information, September 2002.
* Padma-Nathan H, Giuliano F. *Urol Clin NorthAm* 2001; **28;** 321-334.
† Cialis™ (tadalafil) EU prescribing informastion, March 2003.
‡ Lavitra (vardenafil) EU prescribing information, March 2003.
C_{max} = change in maximum plasma concentration
t_{max} = time to maximum plasma concentration
t1/2 = plasma half-life
nd = not determined

effective therapy to patients. The main adverse effects are nausea and vomiting, which become less after repeated use.

Patients who fail first-line therapy may respond to second-line therapy in the form of intra-urethral instillations and intra-cavernous injections. Intra-urethral prostaglandin E_1 (Medicated Urethral System for Erection or MUSE) or intracavernous injection in the form of prostaglandin E_1 (Caverject), papaverine or combinations of papaverine and phentolamine (bi-mix) or with prostaglandin E_1 (tri-mix) have been proven effective and safe. The main advantage of their use is the rapid onset of action and low cost.

Implantation of penile prostheses is offered as third-line or last therapy. It has been reported to have a high patient and partner satisfaction rate. Vacuum constricting devices offer safe treatment for high-risk patients and may be used as first-line therapy in these or other patients.

Young men who present with ED after perineal trauma or pelvic fracture may suffer from arterial damage to the pelvic and penile vessels. Investigations for arterial obstruction include vascular evaluation (pharmacodynamic duplex Doppler evaluation of penile blood flow and selective internal pudendal arteriography). When arterial obstruction is confirmed, arterial bypass surgery may be curative. Young men may sometimes present with primary or life-long ED due to venous leaks that are demonstrated by cavernosometry and cavernosography and surgically corrected by venous excision or ligation.

Patients who fail first-line therapy may respond to sec - ond-line therapy in the form of intra-urethral instillations and intra-cavernous injections.

Patients with Peyronie's disease (fibrous plaques, mainly in the dorsum of the penis) usually present with angulations of the penis that make penetration impossible. Some patients may present during earlier stages of the disease with penile pain. Many different treatment strategies have been described for the pain and angulation, but so far none has proved to have a real advantage over non-steroidal anti-inflammatory medication for 3 - 6 months. Patients with angulations respond well to corrective surgery after the disease has stabilised (usually after 12 - 18 months). When erection and penile length are adequate, plicating sutures may be placed in the tunica albuginea on the convex aspect of the angulation, to straighten the curvature (Nesbit's procedure). In patients who have erections but are concerned about loss of penile length, incision and inlay procedures (Horton-Devine or Lue) may be used to correct angulations. Some patients present with loss of distal penile rigidity or a complete loss of rigidity. Loss of distal penile rigidity may be caused by a venous leak at the plaque. This can be demonstrated by cavernosography and corrected surgically. Total loss of penile rigidity due to Peyronie's disease can only be treated with implantation of a penile prosthesis.

Libido problems

Loss of libido or reduced sexual drive has been associated with reduced male hormones. In spite of reports about the weak association between reduced testosterone level and libido, serum testosterone should be tested. The low serum testosterone associated with prolactin-secreting adenomas responds poorly to androgen replacement. After excluding a macro-adenoma or other brain lesion by CT scan, prolactin inhibition with bromocriptine usually results in normal androgen and erectile function.

Low serum testosterone, associated with symptoms of hypotestosteronaemia, can be corrected with transdermal testosterone preparations, intramuscular or oral testosterone replacement. Carcinoma of the prostate must be excluded, as should benign prostatic hyperplasia. Evidence is accumulating in favour of treating the symptoms associated with androgen decline in the ageing male with restoration of bio-available testosterone levels

to physiological values with the aid of transdermal preparations.[8,9]

Ejaculatory problems

Rapid ejaculation, the preferred term for premature ejaculation, is the most common cause of erectile failure. In the young sexually uninitiated male, rapid ejaculation is normal, with an increase in ejaculatory time with experience. Patients with persistence of rapid ejaculation that prevents satisfactory sexual experience may be treated with measures to reduce sexual anxiety, such as the squeeze technique or the silent vagina. In cases where rapid ejaculation persists, tricyclic antidepressants or serotonin reabsorption inhibitors may be used to increase the ejaculatory time.

FEMALE SEXUAL DYSFUNCTION (FSD)

The most contemporary definition and classification system of FSD resulted from an international consensus panel in 1998.[10] FSD was expanded to include both psychogenic and organic causes of desire, arousal, orgasm and sexual pain disorders and is set out in Table II.

Epidemiology

The epidemiology of FSD is influenced by the populations studied. Reliable prevalence estimates can only be obtained from well-designed population studies. These are influenced by many factors such as age, socio-economic status, marital status and availability of a sexual partner, partner limitations, concurrent illnesses and others. Lack of adjustment for all factors may lead to distorted estimates.

Due to a lack of longitudinal data, there are no published incidence estimates of FSD from well-designed, longitudinal, population-based studies. According to the NHSLS, overall prevalence of FSD in USA women aged 18 - 59 years was 43%.[11] Low desire was reported by 22%, arousal problems by 14% and sexual pain by 7%, using categories similar to the MMAS defined by LCA. In general, sexual dysfunction was more common among younger women, except for trouble with lubrication. Older women were less likely to have sex when their partner had poor health or if they had low feelings of self-worth. Lack of activity does not imply sexual dysfunction for older women. Although about one-third of women in the UK had at least one operationally defined sexual dysfunction, only about 10% of them thought they had a sexual problem. This may explain why only a proportion of women seek medical attention for these conditions.

Risk factors

The factors identified cannot truly be expressed as risk factors, but as correlates of dysfunction. Most information comes from the NHSLS. In contrast to men, age is

Table II. Female sexual dysfunction as defined by the International Consensus Development Conference on Female Sexual Dysfunction

I. Sexual desire disorders
IA. Hypoactive sexual desire disorder
Hypoactive sexual desire disorder is the persistent or recurrent deficiency (or absence) of sexual fantasies/thoughts, and/or desire for, or receptivity to, sexual activity, which cause personal distress
1B. Sexual aversion disorder
Sexual aversion disorder is the persistent or recurrent phobic aversion to and avoidance of sexual contact with a sexual partner, which causes personal distress

II. Sexual arousal disorder
Sexual arousal disorder is the persistent or recurrent inability to attain or maintain sufficient sexual excitement, causing personal distress. It may be expressed as a lack of subjective excitement or a lack of genital (lubrication/swelling) or other somatic responses

III. Orgasmic disorder
Orgasmic disorder is the persistence of recurrent difficulty, delay in, or absence of attaining orgasm following sufficient sexual stimulation and arousal, which causes personal distress

IV. Sexual pain disorders
IVA. Dyspareunia
Dyspareunia is recurrent or persistent genital pain associated with sexual intercourse
IVB. Vaginismus
Vaginismus is recurrent or persistent involuntary spasm of the musculature of the outer third of the vagina that interferes with vaginal penetration, which causes personal distress
IVC. Non-coital sexual pain disorder
Recurrent or persistent genital pain induced by non-coital sexual stimulation

inversely associated with sexual dysfunction in women. Younger age was a significant predictor for pain during sex, lack of pleasure and anxiety about performance. Lower level of education was more often associated with pain during sex. Low desire was more common among women who experienced a sexually transmitted disease, those who experienced emotional problems and stress, women with more than 20% drop in household income and those with infrequent thoughts about sex. Arousal disorder was higher among women with a urinary tract symptom, an emotional problem, stress, infrequent thoughts about sex and a history of being sexually touched before puberty or ever being sexually forced by a man. Sexual pain was also more common among these women. Low physical and emotional satisfaction and low general happiness were significant correlates of the sexual dysfunction categories, of low desire, arousal disorder and sexual pain. The Massachusetts Women's Health Study II preliminary results, examining the change in sexual function over a 6-year period of transition from pre- or peri-menopause to post-menopause, indicate that decreased desire is related to increased age, increased body mass and poor self-perceived health and higher desire to starting hormone therapy.

Though inconclusive, studies of sexual dysfunction in women with diabetes suggest increased prevalence of problems such as decreased lubrication and libido that may be related to duration of diabetes and the presence of neuropathy. Although treatment with antihypertensive agents is associated with sexual dysfunction in men, there is little comparable research in women, but there is some evidence of decreased libido and difficulties with orgasm related to antidepressant use in women.

Anatomical and physiological aspects of sexual arousal of the human female genital tract[12]

Stimuli which are psychologically acceptable and physiologically effective can create enough sexual excitement to activate an orgasmic response. These erogenous areas, when stimulated via specific nerve endings, are relayed via spinothalamic, spinoreticular and dorsal column systems of the spinal cord to the brain, where they are interpreted as sexual stimuli and converted into sexual arousal. These structures include the clitoris, peri-urethral 'glans', urethra, G-spot, Halbans fascia, anterior fornix, pubococcygeus muscle and the cervix.

Lower level of education was more often associated with pain during sex.

Physiology

Vaginal lubrication

The vagina is devoid of glands and covered by squamous epithelium, which is surrounded by a sheet of smooth muscles set in a bed of striated pelvic muscle with extensive blood, lymphatic and nerve supply. The nerve supply is richer in the more distal and anterior wall areas, compared with the more proximal and posterior walls and contains a great variety of classic and peptidergic transmitters of which the exact function is unknown. On sexual arousal the blood supply to the vaginal epithelium is rapidly increased by neural innervations via the sacral anterior nerves S2 - S4. The venous drainage is probably reduced simultaneously. This induces a neurogenic transudation that appears as bead-like droplets, rich in sialoproteins, which coalesce and create a lubricative film that can partially decrease the acidity of the vaginal basal fluid within seconds of successful sexual arousal. The enhanced blood flow is activated by vasoactive intestinal peptide (VIP) innervations of the large vessels supplying the epithelium and the transudation possibly aided by calcitonin gene-regulating peptide (CGRP). There appears to be little nitric oxide synthase (NOS) in the blood vessels and it is unlikely that NO is a major factor in vaginal lubrication.

Pelvic and genital muscular activity in the basal and arousal states

The uterus and vagina are active, especially peri-menstrually when the uterus contracts periodically to expel uterine and vaginal contents. Normally the uterine and vaginal contractions are not consciously recognised, except when they reach painful and spasmodic levels (dysmenorrhoeic pain). During arousal to orgasm, the few records available show an increased vaginal luminal pressure. Orgasm is associated with a series of pelvic, clonic, striated muscle contractions which are concomitant with the subjective feeling of orgasm.

Very little is known about the central nervous system pathways controlling sexual function in women. Those available provide comparable sites and nervous projections to those operating in the male.

Evaluation

Patients should be evaluated as a couple and investigations pursued as far as couples require. A detailed history that includes medical, surgical, medication, sexual and psychological history is required. A complete physical examination should be performed, with special attention to the genital area to assess atrophic vaginal

changes, infected peri-urethral and vestibular glands, prolapse and pelvic masses.

A female hormonal profile, including testosterone determination, is always indicated.

Treatment modalities

Hormonal replacement with oestrogen when indicated, e.g. for atrophic vaginitis and deficient vaginal lubrication that may contribute to female sexual arousal disorder (FSAD).[13] Hypoactive sexual desire disorder (HSDD) may be due to deficient androgen. Androgen supplementation has been reported to increase desire and blood flow to the female genital area.

The nitric oxide-cyclic guanosine monophosphate pathway plays a role in female genital (vulvar and clitoral) vasocongestion during sexual arousal.[14,15] PDE type 5 inhibitor (sildenafil) has been reported to increase sensation in the genital area during intercourse or stimulation, with increased intercourse and/or foreplay satisfaction in female patients with FSAD without HSDD, but not in women with FSAD and HSDD.[16]

Local pelvic and vaginal conditions that may affect sexual function or cause dispareunia, should be diagnosed and treated. Some of these conditions, like chronically infected para-urethral and vestibular glands or other tumours, respond well to surgical procedures.[17]

References available on request.