Management of erectile dysfunction

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Abstract

Erectile dysfunction (ED), or impotence, significantly affects men from the age of 18 years but primarily those over 40 years of age. It is defined as the persistent inability to maintain penile erection sufficient for satisfactory sexual intercourse. EDis a multi-faceted condition that may involve any one (or more) of several different organic causes. Conversely, it may also be psychogenic in nature. This article provides an overview of the current classification, risk factors, impact of COVID-19 diagnosis and management of ED.

Keywords: erectile dysfunction, diabetes-induced erectile dysfunction, impotence

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Introduction

Erectile dysfunction (ED) (or impotence) affects men from 18 years old, and it is defined as the inability to obtain or maintain a penile erection that is sufficient enough for sexual intercourse.[1] This may be accompanied by a lack of desire for sexual intercourse, or ejaculatory problems.[2] While it affects 1–10% of men under 40, the incidence rises to 29% in those aged 40–49, 20–40% in men aged 60–69, and 50–100% in men over 70 years of age.[3] It is strongly associated with cardiovascular disease (CVD), diabetes mellitus, hyperlipidaemia, and hyperhomocysteinaemia, among other metabolic and vascular disorders.[4–6] Age is a significant risk factor, with the likelihood of ED increasing as men get older. ED significantly affects quality of life, relationships, and overall well-being.[7]

Aetiology and pathophysiology of erectile dysfunction

Upon evaluating ED, various factors need to be assessed before a suitable treatment can be decided on (refer to Figure 1).

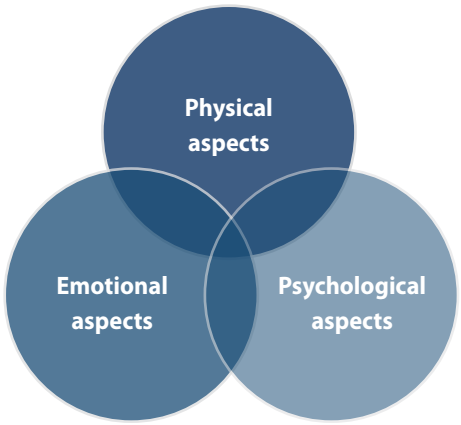

Figure 1: Possible aetiologies of erectile dysfunction[8]

Physical and organic causes

It is essential to address physical or organic causes that may lie at the root of the problem. Major physical and organic causes are summarised in Table I. Neurogenic factors include neurological disorders and neuropathies. The endocrinological disorders have a major impact on hormonal control in males suffering from ED. Androgens are important for sexual desire and maintaining normal sleep-wake erections. However, the latter are not involved in visually induced erections. ED is only reversible or curable in a small number of men, and patients with ED secondary to specific endocrinopathies (e.g. hypogonadism or hyperprolactinaemia) may be curable.[9,10] Certain conditions affect penile arterial supply, which will be classified as vasculogenic ED. These conditions include cigarette smoking, atherosclerosis, hypertension and pelvic irradiation.[11] The microvascular effects of diabetes mellitus can also cause penile arterial insufficiency.[12] Therefore, the pathophysiology associated with diabetes-induced erectile dysfunction (DIED) is multifactorial.[13]

Erectile dysfunction and other health conditions

ED is not just a sexual health issue, it is now recognised as an early marker of several chronic diseases, including CVD, diabetes, metabolic syndrome, and mental health disorders.[6] People living with chronic non-communicable diseases (NCDs) such as diabetes mellitus and CVDs are at significantly increased risk for sexual dysfunction. The estimated prevalence of ED in patients with diabetes in Africa was noted to be as high as 71.45%.[16] Interestingly, ED has been identified as an independent marker for CVD In response to emerging evidence on the risk factors for sexual dysfunction, local guidelines have been adapted to include routine screening of people living with diabetes for sexual dysfunction. Other associated risk factors for sexual dysfunction include

Table I: Physical and organic factors involved in erectile dysfunction[14,15]

Neurogenic erectile dysfunction	Endocrinological erectile dysfunction	Vasculogenic erectile dysfunction	Drug-induced erectile dysfunction	Systemic diseases and general ill health	Cavernous factors (local penile factors)
Central nervous system (cerebral/spinal cord), e.g. following cerebral insult or spinal cord injury, and multiple sclerosis	Diabetes mellitus, hypogonadism and hyperprolactinaemia, hypo- or hyperthyroidism	Arterial: macro- or microangiopathy (e.g. atherosclerosis and trauma)	Refer to Table II	Excessive body weight, especially abdominal obesity (with a waist circumference of > 102 cm in men)	Cavernous fibrosis after priapism or due to other conditions, e.g. Peyronie's disease and/or penile fracture
Peripheral, afferent nervous system (sensory neuropathy, e.g. diabetes mellitus)		Venous: failure of the corporal veno-occlusive mechanism		Smoking, dyslipidaemia, metabolic syndrome, etc.	
Peripheral, efferent nervous system (autonomic neuropathy, or following radical pelvic surgery)		Sinusoidal: fibrosis, failure to relax		Chronic diseases: liver, respiratory and kidney disease	

increased age, depression, mental health conditions, chronic pain, obesity, substance abuse, HIV and certain medications.[16,17]

Erectile dysfunction and diabetes

Several studies have shown that type 2 diabetes (T2D) is associated with lower levels of both total and free testosterone, with an estimated 25–50% prevalence of hypogonadism among affected individuals.[18] The diabetic population exhibits a higher prevalence of metabolic syndrome and obesity, both of which are significantly associated to hypogonadism and ED.[19] As a result, this population experiences health-related declines in quality of life and faces a two to three times higher risk of CVD, independent of age, smoking status, and low-density lipoprotein (LDL) levels. In contrast, individuals with type 1 diabetes (TID) typically maintain normal testosterone levels and rarely develop hypogonadism. It is estimated that ED affects up to 75% of all men with diabetes, it is age correlated and occurs at a younger age in men with diabetes.[12,13]

Erectile dysfunction and cardiovascular diseases

ED is an early manifestation of CVD. In addition to the sexual distress, ED has been identified as a potential early indicator of CVD, which remains the leading cause of mortality globally.[20] This is attributed to the fact that both ED and CVD are vascular disorders sharing common risk factors and underlying pathophysiological mechanisms, including endothelial dysfunction, chronic inflammation, and reduced plasma testosterone levels.[5] Because penile artery size is smaller compared with coronary arteries, the endothelial dysfunction results in a more pronounced reduction in blood flow to erectile tissues than to the coronary circulation.[21] From a clinical standpoint, because ED may precede CVD, it can be used as an early marker to identify men at higher risk of CVD events.[20]

Psychological and emotional components

Several factors can contribute to an increased risk of ED, including lifestyle choices, genetic predisposition, neurological and psychiatric disorders, medication use, and CVDs.[21] However, psychological factors have also been found to play a crucial role in the onset and severity of ED. Stressful life events can be the cause of sexual dysfunction; these may include daily worries about money, work or other significant occurrences.[22] This may be due to the activating and inhibiting mechanisms of the sympathetic and parasympathetic nervous systems. During stressful times, the sympathetic nervous system will release adrenalin, which may counteract the effects of the parasympathetic system on sexual arousal and, therefore, instead of becoming sexually aroused, the penis may be flaccid or not sufficiently erect.[23] Not only will sexual dysfunction have an effect on the individual but also on the couple. Partners of men suffering from sexual dysfunction also

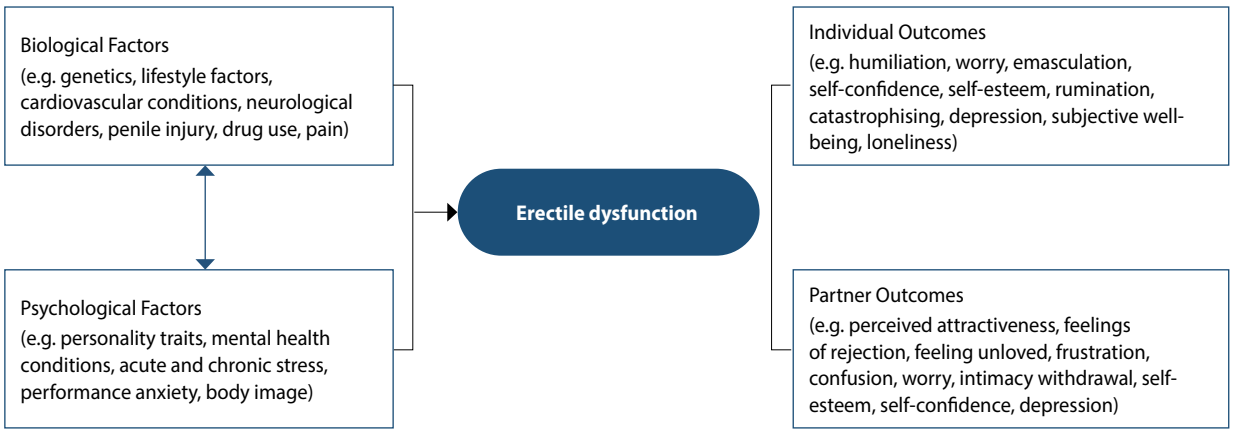

Figure 2: A general model illustration of key psychological contributors and outcomes of erectile dysfunction[24]

suffer in terms of their quality of life. ED may lead to friction in a relationship and when the ED is cured, the quality of life may markedly be increased for both partners. A general model of psychological processes in the experience of ED is illustrated in Figure 2.

An important causative factor for the pharmacist to consider is drug-induced ED. Table II provides a checklist for the pharmacist to review prescriptions when working with patients presenting with ED. The drug classes most commonly associated with drug-induced ED include psychotropic drugs (i.e. the tricyclic antidepressants, selective serotonin-reuptake inhibitors, phenothiazines and butyrophenones) and antihypertensive agents (i.e. the thiazide diuretics and β-blockers) amongst others (refer to Table II).[25,26] The β-blockers have distinct variations within the class, with metoprolol and carvedilol being associated with higher rates of ED, atenolol and bisoprolol with intermediate rates, and nebivolol with the lowest rate of ED.[27] Patients treated with a β-blocker also seem to have a lower number of sexual encounters per month when compared to placebo.[27]

Systemic diseases and general ill health involved in ED include a sedentary lifestyle (i.e. the absence of any physical activity for at least 30 minutes twice a week), smoking, hypertension, metabolic syndrome, other heart diseases (e.g. angina, heart failure, etc.), and dyslipidaemia amongst other conditions.[28]

Ageing has, however, been identified as the primary risk factor for ED. As life expectancy increases, morbidity and disability increase as well. In the ageing male testosterone, dehydroepiandrosterone (DHEA) may decrease together with increased levels of follicle-stimulating hormone (FSH) and luteinising hormone (LH). Even if the testosterone levels are normal the availability to tissues (i.e. the free testosterone levels) may be decreased.[29] In older males, the main areas of sexual dysfunction that are subsequently affected are a lack of sexual desire (or libido) and erectile problems.

Table II: Drugs and other substances involved in erectile dysfunction – a checklist for the pharmacist

Drug involved	Check ✓
Psychotropic drugs	
Tricyclic antidepressants, e.g. amitriptyline, imipramine, clomipramine, dosulepin, lofepramine and trimipramine	☐
Selective serotonin-reuptake inhibitors, e.g. citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine and sertraline	☐
Phenothiazines, e.g. chlorpromazine, trifluoperazine, fluphenazine and prochlorperazine	☐
Butyrophenones, e.g. haloperidol and droperidol	☐
Antihypertensives	
Thiazide diuretics, e.g. hydrochlorothiazide	☐
β-blockers, e.g. metoprolol, carvedilol, etc.	☐
Antiarrhythmics	
Digoxin	☐
Amiodarone	☐
Disopyramide	☐
Antiandrogens	
Gonadotropin-releasing hormone agonists (leuprolide, goserelin and zoladex)	☐
Oncochemotherapy (cyclophosphamide and busulfan)	☐
Flutamide, bicalutamide, cyproterone	☐
Ketoconazole	☐
Spironolactone	☐
Cimetidine	☐
Recreational substances	
Marijuana	☐
Opiates	☐
Cocaine	☐
Nicotine	☐
Alcohol	☐

Diagnosis

The diagnosis of ED (also refer to Figure 3) is based on a thorough assessment, which begins with a basic work-up to identify both modifiable and non-modifiable risk factors associated with the patient's sexual dysfunction.[30,31]

The assessment also involves questioning on the extent of the ED, which may include a question like: *Do you have erection problems (hard enough) during sex?* These questions may provide a positive diagnosis (for more sample questions refer to the International Index of Erectile Function).[32]

Upon confirmation of ED as a diagnosis, the ED can be characterised as either being a primary condition, or existing as a result of another sexual disorder; whether it has always been present or does it vary according to the situation. Assessing if the patient still has spontaneous nocturnal and/or morning erections, and/or in reaction to specific situations (i.e. whether there are good quality spontaneous erections) will rule out physiological causes and indicate that the primary cause of the ED could be psychological in origin.[31]

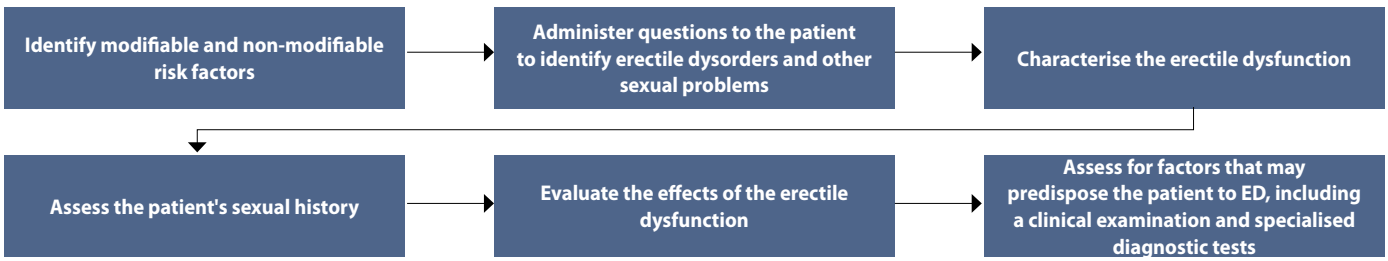

Figure 3: Diagnostic investigations into erectile dysfunction[30,31]

The sexual history should also be assessed, taking into consideration the patient's age, sexual orientation, marital status and previous sexual experiences. The diagnosis should be confirmed with a physical examination to assess the genitourinary anatomy as well as the endocrine, vascular and neurological systems. The physical assessment might also include a more comprehensive cardiovascular examination to measure the heart rate, blood pressure and abdominal circumference.[30]

Laboratory assessment is recommended but not always necessary and may include the following diagnostic tests, based on the patient's medical history as well as the physician's assessment:[30]

- Fasting glucose
- Lipid profile
- Hormone levels, e.g. testosterone, thyroid function, prolactin and luteinising hormone.

Some patients might need further specialised diagnostic tests such as nocturnal penile tumescence and rigidity (NPTR) studies, intracavernous injection test (using a vasoactive agent). This may provide some information on the vascular status of the male and a dynamic duplex ultrasound penile blood flow evaluation.[30] Other tests might include a dynamic infusion cavernosometry/cavernosography for assessment of venous leakage and an internal pudendal arteriography, with this being the most invasive diagnostic test for vasculogenic ED.[30,31] Most of the patients presenting with ED may only need a basic diagnostic work-up, and only in selected cases will more invasive diagnostic procedures be called for.

Management of erectile dysfunction

The effective interplay between four vital factors determines whether a man can achieve and maintain a satisfactory erection for sexual intercourse (see Figure 4). Anatomically the penis is made up of three tube-like structures, namely the ventral *corpus spongiosum* (which surrounds the male urethra and culminates in the glans or tip of the penis), and two dorsal corpora cavernosa. For an erection to occur, the corpora need to become engorged with blood; this necessitates sufficient arterial blood supply to the erectile tissue with a simultaneous occlusion of venous drainage from the corpora.

In terms of nervous system function, the central nervous system (CNS) integrates external sexual stimuli in the medial preoptic area

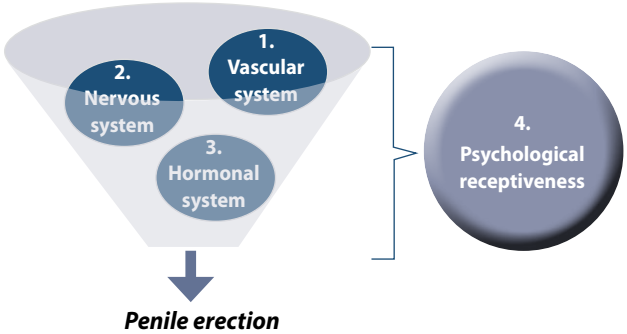

Figure 4: Vital factors that determine normal erectile functioning[32]

of the hypothalamus, where dopamine acts as a proerectogenic neurotransmitter, and is opposed by alpha-2 adrenergic stimulation that results in penile flaccidity.[32]

The autonomic nervous system also plays a vital role in normal erectile functioning, with the parasympathetic nervous system being responsible for achieving the erection via the actions of acetylcholine and the second messengers, cyclic guanosine monophosphate (cGMP) and cyclic adenosine monophosphate (cAMP).[33] Conversely, the erect penis will return to a flaccid state through the actions of noradrenaline (i.e. sympathetic nervous system stimulation) via alpha-2 receptor stimulation, which results in both vascular smooth muscle contraction with a resultant decrease in arterial blood flow in to the corpora and contraction of the sinusoidal (erectile) tissue of the corpora. Some erections may also be the result of a sacral nerve reflex arc, such as the normal nocturnal erections that occur during the sleep cycle. Note that nitric oxide (NO), released from non-adrenergic, non-cholinergic (or NANC) nerves and endothelial cells, also plays a vital role in facilitating a normal penile erection.[32]

Normal testosterone levels are positively linked to normal sexual drive and desire (i.e. libido). ED may therefore develop as a secondary consequence of hypogonadism, which causes decreased testosterone levels. Organic ED results from abnormalities in the vascular, hormonal or nervous system. On the other hand, a lack of psychological receptiveness to sexual stimulation will be classified as psychogenic ED. On average only one in five men with ED suffers from the latter form, with the vast majority of patients having organic causes.[32]

The main aim of ED treatment is to restore and maintain an adequate penile erection for sexual intercourse.[34] As previously mentioned, normal penile erection is a neurovascular phenomenon controlled by psychological factors and coordinated by the endocrine, vascular, and nervous systems.[35] The management of ED involves lifestyle modification such as losing weight, reducing alcohol intake, and avoiding smoking to reduce the impact of comorbid vascular risk factors, and treatment of organic or psychosexual dysfunction with either pharmacotherapy alone or in combination with psychosexual therapy.[36,37] However, pharmacotherapy is perceived as more effective and cost-efficient than the psychosexual therapy.[22] Thus, this review will mainly focus on pharmacotherapy. The pharmacotherapy of ED is classified into two categories i.e. those acting at the local level, and those acting at the central level.[34]

Those acting at the local level mainly aim to either facilitate the relaxation or to reduce the contraction of cavernous smooth muscles.[34] However, those acting at the central level mainly aim to either increase the activities of neurotransmitters/neuropeptides that facilitate penile erection, or to reduce the activity of those that inhibit sexual response.[34] The current pharmacotherapy of ED mainly includes oral phosphodiesterase 5 inhibitor (PDE5I), intracavernosal injection, hormonal replacement therapy, vacuum erection device, penile prosthesis, low-intensity extracorporeal

shock wave (Li-ESW), and stem cell injection therapy.[36]

Phosphodiesterase 5 inhibitors

PDE5Is are regarded as the first-line treatment of ED. Currently, there are seven PDE5Is, i.e. avanafil, lodenafil, mirodenafil, sildenafil, tadalafil, udenafil, and vardenafil with different dosages and formulations.[38] There are three PDE5Is currently available on the South African market, namely sildenafil, vardenafil and tadalafil. Note, however, that these drugs cannot bring about an erection, but rather require the presence of sexual stimulation. The choice of PDE5I is dependent upon the patient's needs and experience with the agent in question. They differ in terms of their onset and duration of action, as well as their adverse event profile, and therapy may be tailored to either meet an on-demand need, or alternatively, to be used daily (i.e. as a chronic treatment option, which could even result in a curative outcome in the presence of endothelial dysfunction).[39,40]

The most frequently-reported side effects are headache and facial flushing. These drugs act by inhibiting the phosphodiesterase isoenzyme (PDE5) that is responsible for the inactivation of cGMP in the cavernous smooth muscle of the penis.[41] It is well established that during sexual arousal, NO is released from the nerve terminals and endothelial cells in the corpus cavernosum.[42] The NO is known to convert guanylate cyclase to convert guanosine triphosphate (GTP) into cGMP, which induces the smooth muscle relaxation and increased blood flow to the penis. However, within the smooth muscle cells of the corpus cavernosum, there is an enzyme known as phosphodiesterase 5 that cleaves and degrades cGMP into 5'-GMP. The degradation of cGMP will result in the termination of signal transduction essential for the stimulation and maintenance of erection.[43,44] Thus, compounds that potentiate NO-cGMP cell signalling system via the inhibition of PDE5 activity have been developed. By inhibiting PDE5, the PDE5Is restore and maintain the erectile response to sexual stimuli by selectively preventing the degradation of cGMP in the corpus cavernosum.[43] When considering a suitable treatment approach, a distinction will be made between organic and psychogenic ED, since the latter requires psychosexual therapy, whereas the organic causes are varied, but would need targeted therapeutic approaches that may combine both non-pharmacological and pharmacological treatment options. The non-pharmacological options include surgery in selected cases (a penile revascularisation procedure could, for example, benefit a younger patient who suffers from a trauma-related vascular injury to the penile arterial blood supply), or the use of a VED, also referred to as a vacuum constrictive device (VCD). Lifestyle modification may also be of benefit to patients who have risk factors that include cigarette smoking, the consumption of alcohol, obesity and a sedentary lifestyle. The oral PDE5Is constitute the current first-line pharmacotherapeutic agents, followed by intracavernosal injections and transurethral therapy as the second-line options.

Intracavernosal injection

The option of directly injecting a vasodilator into the corpus cavernosum is considered to be a second-line treatment for ED.[45] Alprostadil, or prostaglandin E_1, is the only agent with a registered indication for ED in this setting. Patients and their partners, if preferred or required, need to be trained on the proper technique of injecting such agents into the penile shaft.[45] These injections facilitate penile erection, even in the absence of sexual arousal, and may also prove to be of obvious benefit to men with spinal cord injuries or those who had to undergo radical prostatectomies. The two most commonly-encountered adverse effects associated with intracavernosal injections are priapism and penile fibrosis. Both of these adverse effects may be avoided through the use of proper patient counselling and by closely monitoring the patient's progress and response to treatment.[46]

Hormonal replacement therapy

Testosterone-replacement therapy should only be used in cases where deficient levels of the hormone have been confirmed.[40]

Vacuum erection device

The non-pharmacological options include surgery in selected cases (a penile revascularisation procedure could, for example, benefit a younger patient who suffers from a trauma-related vascular injury to the penile arterial blood supply), or the use of a VED also referred to a VCD.[47]

Penile prosthesis

Surgical implantation of penile prosthetic devices may also be an option, especially in men for whom pharmacotherapy has failed. Penile prostheses are regarded as third-line treatment options for ED. These prostheses may be either semi-rigid or inflatable.[48]

Low-intensity extracorporeal shock wave

Although the oral therapy with PDE5Is has been used as the first-line treatment for erectile dysfunction, some patients respond poorly to these medications. As a result, alternative non-surgical treatments, such as low-intensity extracorporeal shockwave therapy (Li-ESWT), have been explored.[49] Li-ESWT is non-invasive and uses acoustic waves, which can pass through tissue and be focused to target specific areas or organs to induce the desired effects. The major potential advantage of this therapy is the possibility to restore natural erectile function improving sexual life of affected individuals.[49,50]

Stem cell injection therapy

Stem cell therapy (SCT) is being explored as a potentially alternative approach for patients with ED who are unresponsive to PDE5Is.[51] It involves the use of stem cells to regenerate damaged or diseased tissues in the penis, with the goal of restoring erectile function. SCT is believed to work through several different pathways, including neovascularisation, anti-inflammatory effects, tissue regeneration, and neuroprotection.[51,52] The current evidence supporting the use of SCT for ED is primarily based on preclinical studies and small, uncontrolled clinical trials (Level 3–4 evidence).[51,52] There is also

considerable variability in the types of stem cells used, delivery methods, and outcome measures, which makes it difficult to draw definitive conclusions. While SCT has demonstrated some benefits in improving erectile function in some studies, further studies are needed to provide valuable insights into the optimal use of SCT and its potential as a therapeutic option for ED.[51,52] The combination of different regenerative treatments, like SCT with low-intensity shockwave therapy or platelet-rich plasma (PRP), may offer more effective solutions for ED.[51] For instance, a study has shown that combining low-intensity shockwave therapy with PRP injections not only improved erectile function but also prolonged the time to ejaculation. These combination approaches are promising and deserve further research.[54]

Psychological interventions and the importance of counselling

Psychological interventions can enhance treatment adherence, integrate the treatment into sexual relationship, and address psychological factors such as anxiety, negative thought patterns, emotional distress, low self-confidence, intimacy issues, and communication difficulties between partners.[22] Through cognitive-behavioural techniques, individuals learn to address performance anxiety, challenge negative beliefs, and enhance communication skills within a relational context.[22] This approach not only improves sexual function but also fosters resilience against future episodes of ED by promoting healthier coping mechanisms and reducing psychological distress. Psychoeducation and counselling, medication interventions and behavioural strategies are common treatment approaches. There are specific assessment and treatment guidelines for ED in men.

The impact of COVID-19 on erectile dysfunction

In 2020, the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spread worldwide at an unprecedented pace.[55] Although research on the link between COVID-19 and ED is still insufficient, there has been increasing evidence of this association over the past two years.[55] A study identified the presence of SARS-CoV-2 in the vascular endothelial cells of the penis, which are essential for erectile function, in post-COVID-19.[55] Additionally, there was reduction in nitric oxide synthase (NOS) expression which was noted in the corpus cavernosum, which is likely a consequence of endothelial dysfunction.[56] Another factor that influenced overall sexual health, and consequently ED may be the fear of COVID-19 infection, particularly concerns about virus transmission during sexual activity.[58] Some studies suggested that stress, anxiety, and depression were the primary psychological factors which were investigated during COVID-19, and they may have contributed to the development of sexual dysfunction.[55,57,59]

Conclusion

ED is a multi-faceted condition that may involve any one (or more) of several different organic causes. These may belong to the vascular, hormonal or nervous system, or a combination of more than one of them. Conversely, psychogenic ED is the result of psychological factors that reduce an individual's sexual responsiveness and desire. Pharmacotherapy may prove to be highly effective in the management of organic ED, with the oral PDE5Is being the current first-line treatment options of choice. The pharmacist could play a significant role in health promotion within the ED setting, through counselling, the identification of modifiable risk factors including drug-induced ED and drug interactions as well as through health education on the proper use of the various treatment options.

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