ERECTILE DYSFUNCTION: THE MALE STIGMA

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ABSTRACT The inability to achieve and maintain a penile erection during sexual activity is a devastating male sexual disorder termed as erectile dysfunction (ED) that affects the psychosocial status of men irrespective of their age. The disease might be of psychogenic or organic origin but the psychological and social burden of the disease is enormous. This factor has kept the disease under-reported and undiagnosed in most of the cases. However, recent awareness and sensitization have encouraged people to discuss the disease and seek clinical help. The diagnosis of ED relies mostly on analyzing patients’ clinical and psychological history than laboratory-based diagnostic tests. In most cases, a questionnaire-based survey is taken to understand the psychological and sexual activity status of the patient. With the advent of modern pharmacotherapy and other invasive procedures, ED has become a manageable disease. The treatment regime may include endocrine therapy, shockwave therapy and in some cases can even require penile prosthesis surgery depending on the extent and severity of the disease. However, lifestyle modification and psychological counseling remain a common support for all patients suffering from ED. An in-depth understanding of the pathophysiology and psychosomatic pattern of erectile dysfunction can help both the patient and the clinician to deal with this disorder and evolve with better options for the management of the disease in future.

KEYWORDS erectile dysfunction (ED)

Key Points
- Erectile dysfunction (ED) is a male sexual disorder associated with an enormous so-cial and psychological stigma.
- Normal erectile physiology depends on myriads of complex physiological functions including hormonal, vascular and neurological processes.
- ED can be of two etiological origins-psychogenic and organic.
- Diagnosis relies solely on the patient’s sexual and psychological status.
- Different management strategies, including pharmacotherapy, hormonal therapy, shock wave therapy and surgical treatments, are available for treating ED patients.

Introduction
Depending on the presentation and clinical manifestation, the definition of erectile dysfunction (ED) can be stated as “the inability to achieve and maintain a penile erection adequate for satisfactory sexual intercourse”[1]. Irrespective of age group the problem of ED is widely distributed in a large portion of sexually active men posing a severe threat to the quality of life. The depth and severity of the problem can be well understood from the size of the population affected by this public health issue. Data reveals that more than 30 million people suffer from ED in the United States [2].

Owing to the stigma and psychosocial concern associated with this disease, many used to hide and hesitate to seek medical assistance for the same. However, with an increasing public sensitization programme and availability of effective therapy, people are seeking primary care consultation for the dysfunction, and consequently, referral to secondary care has also been increased.
To establish the importance of addressing the sexual health, the World Health Organization states that "Sexual health is fundamental to the physical and emotional health and well-being of individuals, couples, and families, and to the social and economic development of communities and countries [3]." ED not only affects the sufferer but leaves a significant impact on the psychology of the partner affecting the relationship and social bonding.

**Epidemiology and prevalence of erectile dysfunction**

ED has already been widely recognized as a significant public health concern affecting the interpersonal relationship, quality of life and psychosocial structure. Thus, the number of people seeking medical assistance for ED and other sexual disorders is increasing these days. In spite of such severity of the problem, the epidemiological data for ED is scarce [4].

Often, the problem of ED is ignored or overlooked as it is not a life-threatening condition. Especially in developing countries, people rarely seek clinical help for ED as it is associated with a stigma [5]. The perception of ED is also varied in the different age group. Younger men often think it will resolve on its own with time, and older men think that it is a normal consequence of ageing. Both the age group tend to overlook the clinical factors associated with it.

With the all available data, it is evident that almost 50% of men in the age range 40-70 years have some degree of ED.

The age-adjusted prevalence rates of ED is reported to be 57.4% in the primary care facility in Nigeria, 63.6% in Egypt, and 80.8% in Pakistan [6]. A retrospective cross-sectional observational study in India reports that 41% of the ED cases belong to the age group of 30-39 years [7]. The global prevalence of ED in men younger than 40 years is 2% whereas this mounts up to 86% in men of 80 years or older [8].

The primary pathophysiology associated with the ED is an impaired flow of blood to erectile tissue or neurological perturbations. In Massachusetts Male Aging Study (MMAS), a survey conducted among the community of non-institutionalised men in the age group of 40 to 70 years revealed that 52% of men are suffering from ED [9]. In a similar study, the National Health and Social Life Survey (NHSLS) reported an increasing prevalence of ED with age. The study showed the prevalence is 7%, 9% and 18% for the age groups 18-29 years, 30-39 years, and 40-49 years, respectively [10].

Taking into consideration this startling prevalence and striking adverse impact on the psyche and quality of life of men, ED remains a severe public health concern across the globe. Until the recently developed awareness and therapeutic module, ED remained a primarily ignored condition among men. However, despite this advancement in the diagnostic and therapeutic font, the various aspect, especially the interconnection of psychosomatic response is still poorly understood by the general population and healthcare personnel.

**Normal Erectile physiology**

The process of erection is guided by an array of physiological cascade guided by the endocrine, vascular and neurological system. Above all, the whole complex process is largely influenced by psychological aspects. Normal male sexual function progresses through the following four stages:

- Desire
- Erection
- Ejaculation
- Detumescence

Also, both the erect and flaccid penile states go through two phases, the initiation, and maintenance. The endocrine pathway responsible for the penile erection is also involved for the state of penile flaccidity and also for maintaining the penile cavernosal integrity.

As stated earlier, the erection follows a cascade of event regulated by the concerted function of psychologic, neurologic, endocrine, vascular, and local anatomic systems. The event of erection is guided by specific parts of the brain, including the hypothalamus. Positron emission tomography (PET) scanning studies showed that sexual arousal is activated in higher cortical centres. Afterwards, it stimulates the medial preoptic and paraventricular nuclei of the hypothalamus. This neurological impulse is ultimately propagated through a complex neural network involving the parasympathetic nervous system and eventually activates the parasympathetic nerves in the sacral area (S2 to S4).

Consequently, this signal results in the inhibition of adrenergic tone and the release of the nonadrenergic, noncholinergic (NANC) neurotransmitter nitric oxide. NANC nerves and endothelial cells are believed to be the source of nitrous oxide, which subsequently stimulates the guanylate cyclase enzyme system in penile smooth muscle. This enzyme enhances the synthesis of cyclic guanosine monophosphate (GMP) which is responsible for smooth muscle relaxation, enhancement of arterial inflow of blood, and venous occlusion. All these events taken together produce the adequate firmness in penis required for sexual activity.

Classification of the erectile pattern is based on its origin and physiology. It is mostly divided into three types: psychogenic, reflexogenic, and nocturnal. Psychogenic erection is majorly controlled by the brain. The sexual arousal in psychogenic erection is guided by visual, sensory, or cognitive stimuli initiated by dedicated parts of the brain. A reflexogenic erection results from tactile penile stimulation and is essential in maintaining the erection during sexual activity.

**Pathophysiology of erectile dysfunction (ED)**

Many classifications have been proposed for ED by several studies based on the aetiology (diabetic, iatrogenic, traumatic) and neurovascular mechanism of the erectile process. Some of the mechanisms associated with ED are the failure to initiate (neurogenic), failure to fill (arterial), and failure to store (venous).

**Etiologies of ED**

The major causes of erectile dysfunction are classified into two major categories: Psycho-ogenic and Organic (Table 1).

**Psychogenic:** Earlier, most of the ED cases were thought to be of psychogenic origin, i.e. originated from psychological factors. With the advent of modern diagnostic techniques and advance re-search, it was found that up to 80 percent of cases have an organic origin. Psychogenic erectile dysfunction originates mostly from relationship stress, performance anxiety, or overt psychological disorders (depression or schizophrenia). The ED is often exacerbated as a result of the adverse effect of the pharmacotherapy prescribed to treat these psychological conditions [11].

**Organic:** This type of ED can be further subdivided into vasculogenic, neurogenic and hormonal etiologies.
Vasculogenic: Vasculogenic etiologies are mostly associated with arterial or inflow disorders. Abnormalities with venous outflow (a corporeal venous-occlusive mechanism) are much less common. A psychological influence always co-exists with the primary etiologic factor.

Neurogenic: An injury or trauma to the spinal cord may hamper the initiation and maintenance of a penile erection. There are several other neurological such as Parkinson’s disease, Alzheimer’s disease, multiple sclerosis, strokes etc. that might lead to erectile dysfunction.

Hormonal: Both primary and secondary hypogonadism is found to be associated with ED. The condition often leads to very low free and total testosterone, which in turn decreases sexual libido and causes erectile dysfunction.

Besides the etiologies mentioned above, consumption of several common pharmacological agents such as antipsychotics, antidepressants, and antihypertensive etc. leads to ED as a common adverse effect.

Often, the terms mild, moderate or complete are used to describe the extent of severity of ED. However, the clinical definition of these terminologies is not precisely described anywhere. Normal erectile ability is just one aspect of male sexual activity. In general, male sexual activity cycle comprises of four major phases:

- Desire
- Arousal (erectile ability)
- Orgasm and
- Relaxation

A clinician’s assessment for a patient complaining about sexual inability largely depends on the identification of the appropriate phase(s) where the dysfunction is actually taking place [11].

Risk Factors

Interestingly, there are several common risk factors for cardiovascular disease (CVD) and erectile dysfunction. Those risk factors are obesity, metabolic disorders, smoking, lack of exercise, diabetes, and hypercholesterolemia.

Several studies have given evidence in support of these common risk factors. For instance, a hypertension-related study in men showed that ED was strongly associated with hypertension [12]. Similarly, a Danish community-based cross-sectional study reported that men with a body mass index (BMI) of 30 or more are prone to have erectile dysfunction [13].

Like CVD, diabetic men pose an increased risk factor for developing ED. The prevalence of ED in diabetic men ranges from 35% to 90%. Also, the onset of ED is 10-15 year earlier in diabetic patients than patients with other risk factors [9].

In contrary to an existing idea, it has been shown that ageing is not an obvious cause of ED. However, it serves as an independent risk factor erectile inability. A survey among a population of 70-year-old men has reported that one-third of the total subjects studied had no difficulty in erection.

Diagnostic Modalities

The preferred, first-line diagnostic test for ED is taking note of history and physical examination. As there is no predefined method of testing ED, the patient’s history and physical assessment lead to an accurate diagnosis in most of the cases. Figure 1 describes the general algorithm for the diagnosis of erectile dysfunction.

Primary assessments

Similar to other diseases, the very first step of the primary assessment is to take a detailed history such as medical and surgical history, sexual history, use of medications and other substances etc. The understanding of psychological and relationship factors is utmost important in a patient’s case history.

The questionnaire used for the survey of sexual history must address the issues such as erection adequacy, altered libido, quality and timing of orgasm, volume and appearance of ejaculate, the presence of sexually-induced genital pain or penile curvature (Peyronie disease), and partner’s sexual function. The severity of ED symptoms is assessed by the standard questionnaire called “The International Index of Erectile Function Questionnaire (IIEFQ)” where five pre-defined items serve as a standard [14].

After that, the patient should be subjected to different physical examination such as meas-urement of blood pressure, body mass index, and waist circumference to assess abdominal obesity etc. A genital examination and an assessment of male secondary sexual attributes are important in diagnosing the cases of ED.

Laboratory tests

The American Urological Association (AUA) and the World Health Organization do not recommend exhaustive diagnostic testing in men for detection of ED. The laboratory tests are mostly meant for assessing the associated risk factors and their influence on ED. Hb A1C or fasting glucose levels are often ordered to determine diabetes. Similarly, a lipid profile, a thyroid-stimulating hormone level etc. is recommended for men to detect hyper-lipidemia or hypothyroidism.
There exists contradictory opinion about routine testosterone measurement in men. Testosterone measurement is only recommended when men are detected with small testes, lack of male secondary sex characteristics, significantly low libido, or a history of inadequate response to phosphodiesterase-5 (PDE-5) inhibitors. It is recommended to repeat the test in a few months interval if the primary result is positive [15].

**Radiologic investigations**

Detection of the adequacy of arterial blood flow in the penile region is crucial in the detection of ED. The evaluation of blood flow direction and velocity can be performed by Penile duplex ultrasonography combined with ICI with Doppler ultrasound. This is the widely used method to determine arterial insufficiency and venoocclusive dysfunction [16].

This specialized USG examination is indicated in patients with penile or pelvic trauma or in case of a failed response to pharmacotherapy. Moreover, the test is also recommended in patients with a history of Peyronie’s disease or other suspected vascular aetiology. In principle, the test is performed to locate the echogenic area resulted from penile fibrosis [16].

**Additional testing**

There are tests such as Nocturnal penile tumescence examination to differentiate between organic and psychogenic ED. The event of erection actually results in a variation in pressure when the penis is compressed by several bands tied around it. This variation is measured by some device in this test. Any absence or abnormality in nocturnal erection suggests an organic aetiology, whereas a normal result in this test suggests psychogenic cause [17].

The use of angiography is not routinely used to assess the vascular defects in patients with ED. It is limited to traumatic injury cases where vascular reconstruction is indicated.

Another rarely used diagnostic test is performed by intracavernous injection to understand the penile vascular status. However, this test yields hardly useful information and thus not performed anymore.

**Treatment**

Management of ED depends primarily on the proper identification of the specific etiological factors. In addition to the medication, modification of the risk factors such as lifestyle habits should be initiated at the primary level of management. The mode of therapy should be instituted, taking into consideration the safety, efficacy, and invasiveness of the treatment as well as cost and the patient preference. The various treatment regimen used for ED is described in figure 2.

**Lifestyle modifications**

Lifestyle modifications, including regular exercise to lose weight in obese and overweight persons, improved control of diabetes, hypertension, and hyperlipidemia, are recommended as the primary management techniques for ED. Studies have shown that low testosterone levels can be modestly improved by the weight loss process. Cessation of smoking is also highly recommended. Compared with men who have never smoked, the risk of ED is increased by 51% in current smokers and 20% for ex-smokers [9].

**Pharmacotherapy**

Pharmacotherapy or use of medication is prescribed as the primary line of treatment for the management of the ED. The most common form of treatment used is phosphodiesterase type 5 inhibitor or PDE5 inhibitors (PDE5i). These drugs inhibit the function of PDE5 enzymes, thereby maintaining the cGMP-mediated...
smooth muscle relaxation and an increase in penile blood flow. Currently, there are four approved PDE5 inhibitors drugs are available for the treatment of the ED: avanafil (Stendra), sildenafil (Viagra), tadalafil (Cialis), and vardenafil (Levitra) (Table 2). In a recent systematic review, the erectile dysfunction and hypogonadism over the past 20 years were analyzed, and this study proposed that PDE-5 inhibitors should be used as first-line treatment for patients with ED.

The most effective therapy used for the treatment of the ED is called intracavernous injection therapy. However, it was thought to be more effective in patients who have an ED of neurogenic aetiology (18).

Other than the two above stated therapies, synthetic prostaglandin E1 analogue called alprostadil is used widely in the treatment of ED. Presently, two modes of administration are available commercially for this particular drug: the direct intracavernosal route and intraurethral application where a small pellet of the drug is used (11).

Newer pharmacological treatments targeting the alternative pathways and replacing the PDE5 inhibitors are also to treat ED patients. Few prospective drugs in these categories are Dopaminergic agents (e.g. Apomorphine), melancortin receptor antagonist (e.g. Melanotan II and bremelanotide), soluble guanylate cyclase stimulators and activators, and Rho-kinase inhibitors [19].

A promising alternative to the current second-line treatment is the drugs used as topical therapy, eg. Topiglan (Combination of alprostadil and soft enhancer of percutaneous absorption). The topical therapies are a good alternative as they do not require intraurethral or intracavernosal invasion and thus safe and patient-friendly to use [19].

Hormonal therapy
Testosterone replacement therapy is only recommended for use in men with hypogonadism. Hypogonadism can be either due to the testicular failure (primary) or because of the disrup-tion of the hypothalamic-pituitary-gonadal axis (secondary). This hormone modulates the penile erection at the level of the brain, in neural pathways, in pelvic plexus, and also in the level of the corpus cavernosum.

Testosterone replacement therapy should be initiated in the presence of an experienced doctor. Regular monitoring of the level of prostate-specific antigen, full blood cell count, and liver function tests is recommended. However, the role of treatment combining a PDE-5 inhibitor and testosterone in men with hypogonadism is still unclear [20].

Erection Devices and assisted technology
Erection devices such as vacuum erection devices (VED) can be used as the second line of treatment regardless of the cause of erectile dysfunction. A VED is consisting of three com-ponents:

• A cylinder,
• A battery- or manually operated vacuum pump, and
• Constriction rings of varying sizes.

The vacuum pump builds a negative pump pressure (100–225 mm Hg) which causes the passive engorgement of the corpora cavernosa. After this, the constriction rings are placed at the base of the penis to retain blood within the corpora. This device can be used in all ED etiologies; however, the success rate depends on the proper instructions and practice of the patient [21].

Although this technique is practised quite often with patients, it has various complications, including pain, bruising, and penile numbness. In severe cases, if the constriction ring is left on for too long adverse severe events such as skin necrosis can also occur.

Shockwave Therapy
Recently, a novel technique called low-intensity extracorporeal shock wave therapy (LI-ESWT) has been developed for treating patients with ED. This particular therapy restores the normal erectile mechanism. In this particular treatment regime, shock waves are used to generate a pressure impulse, which in turn generates transient micromechanical forces in the deep tissue level, resulting in several biological changes and finally resulting in angiogenesis and revascularization [22].

Penile prosthesis surgery
This is the third-line treatment option for ED patients. In this process, the surgical penile prosthesis is implanted in the penis, when other treatments have been proved to be ineffective. They are of two types:

• The simplest and easiest to implant is the Semi-rigid, malleable prostheses. However, in this type the penis is always erect, making it more difficult to conceal the penis.
• In the inflatable prostheses, two tubes are placed inside the penis that replaces the corpora cavernosa. A pump is set up in the scrotum and also an intra-abdominal reservoir. However, getting an infection or in case of any mechanical failure, this type of prosthesis has to be removed.

The main complication includes scarring, penile shortening, and recurrent infections [23].

Managing Psychogenic ED
Erection dysfunction can also be caused by psychological or interpersonal factors. Moreover, in patients with premature ejaculation, genital pain, or dyspareunia can also lead to psychogenic ED. The similar can also be seen in men who have a previous history of sexual abuse. This type of ED can be cured by psychological counselling [24].

In some patients, ED coexists with depression or anxiety, in these cases, treatment of the mood disorder proves to be useful. Antidepressants such as bupropion, mirtazapine, fluvoxamine can also lead to ED. In these patients also, PDE-5 inhibitors prove to be useful in combination with treatments for mood disorders [25].

Future of ED treatment
With tremendous progress in research on erectile dysfunction, several new treatment options are emerging out for patients who do not respond to standard pharmacotherapy. Stem cell therapy is one such option that shows excellent promise to treat ED. The regenerative and wide differentiation property of adipose, bone-marrow and muscle-derived stem cells are being exploited in the treatment of ED [26].

Similarly, gene therapy shows excellent potential as a future of ED treatment. The advantage lies in the lack of systemic complication as the genetic element can be directly injected into the penis. A gene for the alpha subunit of the human smooth muscle Maxi-K channel (hMaxi-K) has shown the promising result in its first human trial [27].
Table 2: Commercially available phosphodiesterase-5 inhibitors used for the treatment for erectile dysfunction.

<table>
<thead>
<tr>
<th>Medication name</th>
<th>Dosage</th>
<th>Recommended time for the administration</th>
<th>Duration of action</th>
<th>Maximum dosage frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avanafil (Stendra)</td>
<td>50, 100, or 200 mg once daily as needed</td>
<td>15 minutes before sexual activity</td>
<td>5 to 10 hours</td>
<td>Once daily</td>
</tr>
<tr>
<td>Sildenafil (Viagra)</td>
<td>20, 25, 50, or 100 mg once daily as needed</td>
<td>one hour minutes before sexual activity</td>
<td>4 to 5 hours</td>
<td>Once daily</td>
</tr>
<tr>
<td>Tadalafil (Cialis)</td>
<td>10 or 20 mg once daily as needed</td>
<td>at least 30 minutes before sexual activity</td>
<td>36 hours</td>
<td>Once daily</td>
</tr>
<tr>
<td>Vardenafil (Levitra)</td>
<td>10 or 20 mg once daily as needed</td>
<td>60 minutes before sexual activity</td>
<td>4 to 5 hours</td>
<td>Once daily</td>
</tr>
</tbody>
</table>

Conclusion

The cases of ED are often underreported due to the stigma attached to it. However, recent advancement in the diagnosis and therapy has enabled a large number of men to report ED and thus providing a considerable population to study several aspects of the disease. Despite a better understanding of ED than before, several aspects of the disease still warrant further study. The understanding of its psychosomatic association and social impact should be made better in the days to come.

Conflict of Interest

The author declares no conflict of interest including employment, consultancies, stock ownership, honoraria, paid expert testimony, patent application/registrations, and grants or other funding.

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