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The current treatment of erectile dysfunction

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Abstract

Erectile dysfunction (ED) is the inability to achieve and maintain an erection sufficient for satisfactory sexual intercourse. It is the most frequent sexual dysfunction in elderly men and its prevalence increases with age.

Ever since ED was recognized as a real health problem, several treatment options became available and some of them proved to be very efficient. PDE5 inhibitors are the mainstay treatment of ED.

However, other treatment options such as intracorporal injections, surgery, vacuum devices and prosthesis are also available for patients who are unresponsive to PDE5 inhibitors. Since none of the treatment options available so far has proven ideal, research in the field of sexual medicine continues. The aim of this paper is to review the most advances in the treatment of ED.

Keywords: erectile dysfunction, PDE5 inhibitors, alprostadil, vacuum erection devices

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Introduction

Erectile dysfunction (ED) is the inability to achieve and maintain an erection sufficient for satisfactory sexual intercourse. It is the most frequent sexual dysfunction in elderly men and its prevalence increases with age. It has a worldwide occurrence. Studies show that approximately 52% of men aged 40-70 years old are affected to some degree by this disorder. While in young males, under the age of 40 years, ED was initially considered psychogenic, recent studies showed that in 14.8% of the cases the ED is organic (1-3). ED has a great impact on the patient's and his partner's quality of life as it can cause depression and anxiety and it can decrease emotional intimacy and satisfaction within a relationship (4).

Penile erection is a complex neurovascular process which involves neurological, molecular, vascular, endocrine and psychological factors. Visual, olfactory and imaginary stimuli are also important. Sexual arousal releases neuro-transmitters, especially nitric oxide (NO), from nonadrenergic-noncholinergic cavernous nerve terminals, through the action of NO-synthetize. NO activates guanylate cyclase which converts guanosine triphosphate to cyclic guanosine monophosphate which phosphorylates certain proteins and calcium channels, thus leading to inhibition of calcium channels, decrease in cytosolic calcium content and, in the end, vasodilatation and smooth muscle relaxation. As the blood fills the sinusoids, intracorporal pressure increases and the subtunical venules are compressed. The blood is trapped in the corpora cavernosa and the penis becomes erect (5-7).

The most important risk factors for ED are aging, arterial hypertension, diabetes mellitus, atherosclerosis, hypercholesterolemia, smoking, prostatectomy, and drugs.

Discussion

Classification of ED

ED can be classified as psychogenic, organic and mixed. Organic ED can be further classified as neurogenic, hormonal, vasculogenic, drug induced or related to systemic diseases. Mixed ED is the most common form of ED (6, 8).

Psychogenic ED occurs more frequently in young men, under the age of 40 years. It can be associated with depression, performance anxiety, decreased self-esteem, stress in relationship, schizophrenia/ psychosis, lack of sexual arousability, and fear or shame of venereal or dermatological diseases. Compared to organic ED, psychogenic ED has a sudden onset, occurs in patients with psychological disorders or going through major life events, while spontaneous and self-stimulated erections are of good quality (6, 8, 9).

Neurogenic ED is responsible for 10-19% of ED cases. Several neurogenic disorders have been associated with ED. Some patients with spinal cord injuries or perineal trauma do not respond to genital stimulation. Patients with stroke, Parkinson's disease and Alzheimer's disease have decreased libido and are not able to initiate the erectile process. ED is up to three times more frequent in patients with epilepsy. Multiple sclerosis is one of the most prevalent neurologic disorders occurring in young men and in 70% of cases it is associated with ED (3, 6, 10).

Several hormones and endocrine disorders have been associated with ED. Klinefelter's syndrome, congenital and acquired hypogonadotropic hypogonadism are associated with androgen deficiency and decreased libido. Hyperprolactinemia results in secondary hypogonadotropic hypogonadism and ED. Patients with hyperthyroidism and hypothyroidism also have decreased erectile function (3, 6).

Vascular disorders are also frequently responsible for ED. Adequate arterial inflow and venous outflow occlusion are both mandatory in order to achieve an erection. Hypertension, atherosclerosis, diabetes mellitus and trauma are associated with inadequate arterial inflow while veno-occlusive dysfunction is associated with venous leakage. Subclinical perineal trauma is also associated with ED and is probably determined by the occurrence of focal arterial occlusive disease. That is also the case in young men who bicycle more than 3 hours a week (3, 6, 11).

ED can be induced by several drugs through various mechanisms. Antihypertensives like beta-adrenergic blocking agents and thiazide diuretics, antiandrogens like finasteride, NSAIDs, antidepressants like selective serotonin anti-reuptake inhibitors, anxiolytics and neuroleptics are some of the medications most frequently associated with ED (3).

Systemic diseases like diabetes mellitus, chronic renal failure, multiple sclerosis, and generalized atherosclerotic disease can often lead to ED (6).

Erectile dysfunction treatment

Ever since ED was recognized as a real health problem, several treatment options became available and some of them proved very efficient. Lifestyle modifications, oral phosphodiesterase-5 (PDE5) inhibitors, intracorporal injections, topical medication, surgery, vacuum devices, and acupuncture are only some of the treatments available today for ED. However, since all these treatments have limitations, the search for novel therapies continues (12, 13).

Lifestyle modifications

Since ED and coronary artery disease share similar risk factors, it is easy to presume that the same lifestyle modifications required for cardiac disease should be required for ED. According to the European Association of Urology guidelines, lifestyle changes and risk factor management must precede or accompany any pharmacological treatment, patients with cardiac disease and diabetes mellitus having the greatest benefits from these changes (14, 15). Therefore, smoking cessation, weight loss, physical activity, avoiding stress and the use of alcohol and illicit drugs should be recommended to all patients suffering from ED (4).

Gupta et. al performed a systematic review and meta-analysis of controlled trials assessing the effect of lifestyle changes and pharmacotherapy on ED. They included 740 participants from 4 countries and concluded that pharmacotherapy for cardiovascular risk factors and lifestyle modifications are effective in patients with ED (16).

Some authors suggest that administration of over the counter dietary supplements such as Panax ginseng may be beneficial to patients with ED, it is associated with low toxicity and low costs and, with a physician's knowledge, could be included in ED treatment (17).

Phosphodiesterase inhibitors (PDE)

PDE inhibitors are the first-line treatment in patients with ED. Studies show that all PDE inhibitors are safe and effective, especially in men suffering from diabetes, multiple sclerosis, cardiovascular disease and spinal cord injury. PDE5 is specific for to cGMP. It has an abundant expression in corpus cavernosum and determines degradation of cGMP. Inhibition of PDE5 leads to high levels of cGMP, muscle relaxation and, in the end, erection (18).

Sildenafil was the first PDE inhibitor successfully used for the treatment of ED. Even though it is a selective PDE5 inhibitor, it cross-reacts slightly with PDE6, which is mainly found in the retina. For that reason, some patients may experience visual disturbances like altered color perception and "star vision". The onset of action is 30 minutes after the first dose and the half-life is 3-5 hours. Studies show that 69% of patients taking sildenafil will obtain an erection suitable for sexual intercourse, as compared to only 22% of patients taking placebo (12, 18, 19).

Vardenafil is a fast-acting selective PDE5-inhibitor used for the treatment of ED. It has been used successfully in some patients who failed to respond to sildenafil. It has an onset of action of 10 minutes and an average half-life of 4.2 hours.

Caution is advised in patients with prolonged QTc who are taking class 1 and class 3 antiarrhythmics (12, 18, 19).

„Revitalise" was an international observational study which included 1832 patients with ED and metabolic syndrome from 10 countries who were treated with vardenafil. The aim of the study was to investigate the effectiveness and safety of vardenafil in the clinical setting. The authors report that 82.4% of the patients had an increase of at least 4 points in the IIEF-EF score and that after treatment 45.4% had normal erectile function. The authors therefore conclude that vardenafil is a good treatment option for patients with ED and metabolic syndrome (20).

Tadalafil is a selective PDE5 inhibitor which showed no cross-reactivity with PDE6 but some cross-reactivity with PDE11. It is a safe drug which proved its effectiveness in ED occurring in both elderly and young men. It has an onset of 20 minutes and the longest duration of action for this class of pro-erectile agents (up to 36 hours). It can be administered on demand or administered daily, in small doses. Studies showed that 81% of patients treated with tadalafil were able to obtain an improvement in the erection quality, as compared to 35% of patients in the placebo arm (12, 18, 19, 21).

Avanafil was approved by the FDA in 2012. It is a potent competitive inhibitor of PDE5. It is a pyrimidine derivative which is rapidly absorbed and it reaches the maximum concentration in 30-45 minutes (12, 18, 19). Cui et al. performed in 2014 a systematic review and meta-analysis in which they included 1381 patients from randomized controlled studies which compared avanafil with placebo. The authors concluded that patients treated with avanafil 100 mg were more likely to achieve successful vaginal penetration and successful intercourse. The rate of discontinuation due to adverse events was similar in the two groups. Avanafil 100 mg seems to be as effective as avanafil 200 mg. The two concentrations seem to have similar safety profiles but headaches are more frequent in patients taking 200 mg of avanafil (22).

Udenafil is a PDE5 specific inhibitor developed in Korea for the treatment of ED. It also inhibits cGMP hydrolysis. It reaches peak plasma concentrations in 0.8-1.3 hours and is associated with rapid onset and a long duration. It is a well-tolerated, safe, effective treatment for ED. It also proved its efficacy in patients with ED associated with diabetes mellitus, hypertension and lower urinary tract symptoms. It can be administered on demand or daily (12, 23).

Mirodenafil is another selective PDE5 inhibitor developed in Korea for the treatment of ED. Its selectivity for PDE5 is 10 fold higher that sildenafil's selectivity for PDE5. It reaches the peak concentrations after 1.25 hours and it has a half-life of 2.5 hours. It has beneficial effects in patients with ED and lower urinary tract symptoms and benign prostatic hyperplasia. Daily treatment with mirodenafil and on demand treatment are both effective in patients with ED (12, 24).

Testosterone replacement therapy (TRT)

In the past, testosterone was believed to enhance sexual function in males. Currently, however, it has been shown that testosterone is only useful in males with hypogonadism. Hypogonadism usually affects older males and ED is one of its symptoms. Even though TRT has beneficial effects on several of the symptoms related to hypogonadism, data regarding its usefulness in ED is controversial. Some studies suggest that combining TRT with PDE5 inhibitors could be helpful in patients who are unresponsive to PDE5 inhibitors alone. Randomized controlled studies are however necessary to support these observations (25, 26).

Testosterone cypionate is available for intramuscular injections administered every three weeks. As an alternative, testosterone patches and gels are available for daily use (27).

Alprostadil

Alprostadil is a synthetic prostaglandin E1 which has been approved for the treatment of ED. Intracavernous alprostadil injections are a second line treatment in ED. A study performed on 848 men aged 18-75 years old treated with intracavernosal alprostadil showed that the treatment is effective in achieving satisfactory erections and safe (28). Fear of penile puncture and pain restrict the use of alprostadil injections.

Alprostadil urethral suppositories are also a second line treatment in ED. They have the advantage of minimal adverse reaction and drug interactions but their efficacy is lower than that of alprostadil injections and patient compliance is low due to moderate to severe penile pain (6, 29, 30).

Alprostadil cream is an alternative to urethral suppositories and injections. Rooney et. al performed a study in 2009 in which they aimed to evaluate the efficacy and safety of topical alprostadil. The study included 1161 patients with ED who were asked to administer 200 mcg to the penis meatus before intercourse for four weeks. After four weeks the patients were asked to apply 300 mcg if hypo-responsive and 100 mcg if hyper-responsive. The authors concluded that alprostadil

cream was effective and safe for the patients and their partners and the most frequent adverse events were limited to the application site (31).

Other intracavernosal injections

Apart from aprostadil, other substances can also be injected intracavernosally in patients who do not respond to oral treatment with PDE5 inhibitors.

Papaverine has multiple mechanisms of action which make it useful in ED. It is a non-specific PDE5 inhibitor; it decreases resistance to arterial inflow and increases resistance to venous outflow. Its utilization is however limited by its side effects: corporal fibrosis and priapism (6, 12).

Phentolamine is a competitive α-adrenoceptor antagonist which can also determine histamine release from mast cells. It can decrease resistance to arterial flow. It is not very effective in monotherapy. It can cause hypotension and reflex tachycardia (6, 12).

The vasoactive intestinal peptide (VIP) is a vasodilator that stimulates cAMP formation. It failed to prove its efficacy in ED when administered in monotherapy but showed some good results when it was administered with phentolamine (12).

While the efficacy of this class of agents in monotherapy is not very high, when used in combination they act synergistically and are associated with a response rate of up to 90%. The most frequent and effective combination includes papaverine, phentolamine and alprostadil (6, 12).

Stem cells

Stem cells (SC) are intensely studied at present, especially for the treatment of neurogenic ED where available therapies are not very effective. SC can differentiate into endothelial cell, neurons, smooth muscle cells and Schwann cells, among others, and there is hope that once transplanted they might help the regeneration of the injured tissue.

Three types of SC are generally used in ED: adipose tissue-derived SC (ADSC), muscle-derived SC (MDSC) and bone-marrow derived SC (BMSC). The SC can be delivered by intravenous injection, intracorporal injection or intraperitoneal injection.

Studies involving SC were performed on animal models, especially rats, and have shown promising results. Since stem cells might provide a cure for ED and not only symptom relief, the results of clinical trials on men with ED are enthusiastically awaited (13, 32, 33).

Vacuum erection devices (VED)

Even though VED can be used for the treatment of ED of any etiology and have been

recommended by the American Urological Association as an alternative therapy since 1998, they only became more frequently used in the last years, especially in patients requiring penile rehabilitation after radical prostatectomy.

VED produce negative pressure with the help of a vacuum pump. This causes the distension of the corporal sinusoids and arterial blood inflow. A constriction ring is placed at the base of the penis to decrease venous outflow. As a result, the penis becomes erect. In patients with ED due to radical prostatectomy, VED help the recovery of erectile function through anti-hypoxic, anti-apoptosis and anti-fibrotic mechanisms. Some authors suggest that when VED are used for penile rehabilitation, the rubber ring should not be used, as it may lead to fibrosis as a result of prolonged ischemia and acidosis.

Studies show that VED are effective in up to 90% of patients. They allow sexual intercourse soon after surgery and result in early return of natural erections.

VED are non-invasive treatment methods and the most commonly reported adverse reactions are bruising, pain, cold penis or penile discomfort. Caution is required in patients undergoing anticoagulant treatment (10, 34-37).

Surgical management

Surgical treatment is rarely necessary in patients with ED and it is reserved for patients who are resistant to PDE5 inhibitors.

Arterial revascularization has been tried in patients with penile artery insufficiency of various causes but it mostly benefits young men with traumatic disruption of the vasculature. Several technics are available but most commonly the epigastric artery is anastomosed to the dorsal penile artery. The revascularization technique is only effective in 30-50% of cases (6).

More recently, endovascular treatments were tried in patients with vasculogenic ED refractory to PDE5 inhibitors. The Zen Trial (Zotarolimus-Eluting Peripheral Stent System for the Treatment of ED in Males with Sub-Optimal Response to PDE5 Inhibitors) published in 2012 investigated the use of drug-eluting stents in patients with focal atherosclerotic lesions of the internal pudendal artery. The drug they used was zotarolimus, an immunosuppressive agent which prevents restenosis and the rate of neointimalization. Even though the authors obtained some promising results, larger studies are necessary to support the usefulness of the technique (11, 37, 38).

Venous surgery should only be performed in patients with proven venous leakage who have a normal arterial response on duplex Doppler and

who do not have generalized penile venous disease. Surgical ligation of the deep dorsal vein and its collaterals was used in the past but only showed positive results in approximately 25% of patients (6, 11).

In 2013 Aschenbach et. al performed a study on 29 patients with ED due to veno-occlusive dysfunction who were treated with endovascular embolization therapy with N-butyl-2-cyanoacrylate. The procedure was performed under local anesthesia, it was minimally invasive and clinical success was achieved in 88,8% of the patients (39).

Prosthetic surgery is the third-line treatment in patients with ED and is only recommended in patients who have failed or refused other treatments. Patients must be aware that prosthesis surgery is irreversible and physiologic erections will not be possible any more. Two types of prostheses are available: non-inflatable and inflatable. Non inflatable prostheses have the advantage of being more durable and cheaper and the disadvantages of causing permanent erection, and they are difficult to conceal and device erosion can occur. Inflatable prostheses have the advantage that they offer a flaccid state and an erect state and the disadvantage that mechanical failure can occur. Infections are the most important adverse reactions.

The long-term satisfaction rate is very high in patients using inflatable and non-inflatable prostheses. This procedure however is only recommended to select patients who are willing to undergo implantation of a penile prosthesis (6, 40-42).

Other treatment options

Several devices have been produced in the last years for the treatment of ED. External support devices such as penile casts, vibrators, low intensity extracorporeal shockwave, impulse magnetic field therapy or tissue engineering are just some of the novel devices and procedures proposed for the treatment of ED. Further studies are necessary to prove the efficacy of those devices and procedures. However, there are high hopes that some of them might complete the therapeutic arsenal of ED (37).

Conclusions

ED is a frequent sexual dysfunction which affects men worldwide and has a great impact on the patient's and his partner's quality of life. PDE5 inhibitors are the mainstay treatment of ED. Several other treatment options such as intracorporal injections, surgery, vacuum devices and prosthesis are however available for patients who are unresponsive to PDE5 inhibitors. Since none of the treatment options available so far proved ideal, research in the field of sexual medicine continues.

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