Chapter 51
How to treat erectile dysfunction?

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Introduction

Management of erectile dysfunction (ED) varies considerably depending on the etiology. Following a focused evaluation of the ED patients (Chapter 50), therapy can usually be recommended based on the underlying mechanism. In most men, a thorough history, physical exam, and basic laboratory studies should suffice. Further evaluation with more invasive studies may be indicated for specific patient populations (e.g. those with Peyronie's disease, pelvic injury, endocrine disorders, complicated psychiatric disorders. and young males unresponsive to oral agents).

Nonpharmacologic management

Erectile dysfunction could be a sign of cardiac and peripheral vascular disease. Thus, lifestyle modifications that improve cardiovascular health may also improve erectile function. It has been demonstrated that men who lose weight and enhance their physical activity had significant improvement in erectile function. In contrast, men with higher body mass index (BMI) and a sedentary lifestyle are at increased risk to develop ED. In addition, tobacco use increases the risk of ED in a dose-dependent fashion. Other risk factors for ED include hypertension, dyslipidemia, and type 2 diabetes mellitus.

Medications can also have a profound effect on sexual function. Studies have shown that up to 25% of ED presentations are associated with medications. These adverse effects from common medications can range from decreased blood pressure, hormonal alterations, diminished sexual arousal, or central suppressive effects (Chapter 50). Treatment of hypertension is one of the most common causes of medication-induced ED, as nonspecific □-blockers and thiazide diuretics are known causative agents. Other common medications associated with ED include antiandrogens, antidepressants, and other psychotropics. When a medication is identified as the potential cause for ED, cessation should be

considered. If a medication is essential, substitution with a different medication may be considered. For example, use of calcium channel blockers and angiotensin- converting enzyme inhibitors are alternative antihypertensive agents, as both have decreased negative effects on sexual function. Moreover, other antidepressant medications, such as bupropion or venlafaxine, may also have decreased inhibitory effects on sexual function. Care should be taken to first communicate such changes with the patient's primary care provider to avoid the risk of discontinuing essential medications.

Psychosexual counseling

Psychological counseling has been used with success in various subsets of men with ED. In general, men with psychogenic ED are the main beneficiaries of sexual counseling. These men are generally found to be physiologically normal in terms of erectile function but may suffer some cognitive issues that affect sexual function. Interventions include systematic anxiety reduction, interpersonal therapy, sex education, and couples' therapy. Counseling is often utilized in conjunction with pharmacologic strategies to improve outcomes, especially in unmotivated men.

Vacuum erection device

One nonpharmacologic management strategy that aims to physically produce an erection, as opposed to modifying risk factors, is the vacuum erection device (VED). The mechanism of VED creates a negative pressure on the penis to enhance blood engorgement into the cavernous spaces, thus inducing an erection-like effect. VED is often used in conjunction with a penile constrictive band or ring to maintain an erectile state during intercourse. Advantages of the device include its low cost and ability to produce a rigid erection sufficient for intercourse, including engorgement of the glans. Common drawbacks include pain and bruising at the band site, decreased ejaculate volume, including anejaculation in some cases, caused by the constrictive band, and lower penile temperature and sensation. Those negative side effects have led to a low satisfaction rate (30%-70%) and a high discontinuation rate (up to 60%) after one year.

Pharmacologic management for ED

Phosphodiesterase type-5 inhibitors

PDE-5 inhibitors remain the mainstay treatment for most men with ED due to their attributes of effectiveness, simplicity, and non-invasiveness. In 1998, sildenafil citrate (Viagra, Pfizer, New York, NY, USA) was approved by the FDA. Since then, vardenafil (Levitra, Bayer Schering Pharma AG, Berlin, Germany) and tadalafil (Cialis, Eli Lilly, Indianapolis, USA) were approved for use in 2003, followed by avanafil (Petros Pharmaceuticals, New York, NY, USA) in 2012. All four medications have similar efficacy and side-effect profiles. These medications work by potentiating the effect of nitric oxide on cavernosal smooth muscle. Nitric oxide stimulates guanylyl cyclase and leads to elevated cGMP levels. These second messengers then decrease intracellular calcium levels, which leads to smooth muscle relaxation and penile erection. PDE-5 breaks down cGMP to GMP, causing detumescence. PDE-5 inhibitors inhibit this enzyme and maintain cGMP levels, thereby promoting an erection (Fig. 1).

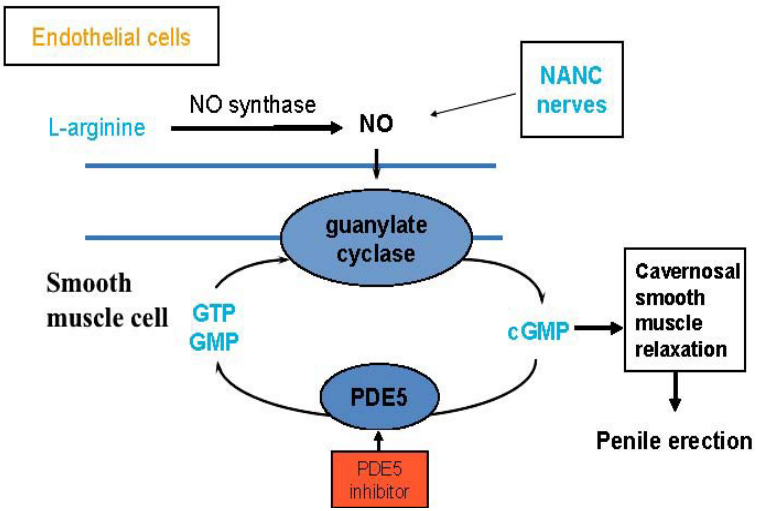

Figure 1. The role of nitric oxide (NO) and cGMP in the physiology of erection and PDE-5 inhibitors in promoting tumescence.

Side effects include flushing, headache, muscle ache, and visual disturbances. These effects are likely due to cross-reactivity with other phosphodiesterases (usually PDE-6 and 11). There have been isolated reports of vision loss following use of PDE-5 inhibitors, known as nonarteritic anterior ischemic optic neuropathy (NAION). Men with retinal conditions, including retinitis pigmentosa, should not use these medications. Vardenafil carries an added warning about cardiac conduction defects, as it may affect the QT interval on electrocardiogram. Therefore, some men taking antiarrhythmics should avoid vardenafil. PDE-5 inhibitors are also contraindicated in men taking nitrates because of the risk of a pronounced drop in blood pressure. Men taking α-adrenergic antagonists for benign prostatic hyperplasia should be cautioned regarding the risk of decreased blood pressure with concomitant use. Patients undergoing radical prostatectomy for prostate cancer and men with diabetes mellitus have shown improvements in erectile function with use. Unless a contraindication for use exists, PDE-5 inhibitors have become first-line therapy in the treatment of all causes of ED.

Intracavernosal or transurethral vasoactive therapies

If PDE-5 inhibitors fail after proper instruction has been given or if a contraindication for use exists, men may consider alternative medical treatments. Intracavernosal injection (ICI) agents have been exploited since 1982. These vasoactive agents, which include alprostadil, papaverine and phentolamine, are injected directly into the cavernosal tissue to produce an erection. Alprostadil (Prostin VR) works by increasing intracellular cyclic AMP levels and decreasing intracellular calcium. It is the only FDA-approved injectable medication for ED and is available under the trade names Caverject (Pfizer, New York, NY, USA) and Viradel/Edex (Schwarz Pharma, Milwaukee, WI, USA). After injection, the medication is locally metabolized by 96% within 60 minutes and produces a full erection at doses of 10 to 20 μg in 70% to 80% of men with ED.[1] Papaverine is a nonselective PDE inhibitor that increases intracellular cAMP and cGMP levels. Phentolamine is an α-adrenergic antagonist that increases presynaptic norepinephrine levels. These medications are used alone or in combination for injection into the cavernosal tissue. Side effects include painful erection, priapism, and increased incidence of cavernosal fibrosis (mainly with papaverine and phentolamine). Men taking anticoagulants should be advised to apply manual pressure for several minutes following injection to avoid hematoma formation.

Intraurethral suppositories, which were developed with the hope of avoiding the invasive nature of intracavernosal needle injection, are another way of administering vasoactive agents into the erectile bodies. Specifically, the vasoactive agents are absorbed into the corpus cavernosum through the mucosal lining of the surrounding corpus spongiosum. A synthetic formulation of alprostadil was developed and approved by the FDA in 1996 as MUSE (Medicated Urethral System for Erection; MEDA Pharmaceuticals, Somerset, NJ, USA). The responder's rate for MUSE is approximately 50%, and men must properly dispense and manually distribute the medication into the penis to optimize success.

Testosterone **replacement**

Studies have demonstrated that hypogonadal ED men show improvement in erectile function with testosterone replacement therapy. In addition, men may have improved responses to PDE-5 inhibitors in combination with testosterone replacement therapy (TRT). These men on TRT should be cautioned regarding the risks of hormonal replacement, including erythrocytosis and possible effects on the prostate. These men should be monitored while on therapy with semi or yearly digital rectal examination (DRE), measurement of serum prostate specific antigen (PSA) and complete blood counts. Any elevation in PSA or abnormal DRE should warrant prostate biopsy to rule out underlying prostate cancer. Men with a history of prostate cancer need to be cautioned about the risks of TRT. Recent studies have reported that TRT is likely safe in men with a history of confined prostate cancer; however, patients should be well-informed and judicious about follow-up. Testosterone replacement therapy can be delivered through injections, transdermal gels and patches, oral formulations, nasal gels, or implantable pellets.

Surgical therapy for ED

Surgical therapy for ED is reserved for patients who fail medical therapy or exhibit an underlying condition unamenable to medical therapy. Surgical therapy involves implantation of a penile prosthesis. The prosthesis may consist of inflatable cylinders or malleable rods. The inflatable devices consist of intracavernosal cylinders with a reservoir and a scrotal pump. In the two-piece device, the scrotal pump and reservoir are self-contained, whereas the three-piece device contains a separate reservoir that is implanted within the pelvis. These devices carry very high patient

and partner satisfaction rates. Risks such as infection or malfunction of the device may necessitate revision or removal. In certain men with documented arteriogenic ED resulting from pelvic trauma, penile revascularization surgery may be indicated. The ideal patients are young men with no risk factors for ED and with documented arteriogenic insufficiency diagnosed with pelvic angiography. Successful revascularization in these patients can result in normal erectile function in the majority of men.

Experimental Therapies

In recent years, there has been an increasing interest in finding a durable therapy for ED. Proposed treatments include platelet-rich plasma (PRP), intracavernosal stem cell therapy, and low-intensity extracorporeal shockwave therapy (Li-ESWT). According to the FDA, these therapies are experimental and need further evidence before regulatory approval.

Intracavernosal Botox injections have been recently explored and yielded subjective improvement by validated questionnaires in recent studies. Other emerging pharmacologic interventions include selective activators of maxi-K channels, guanylate cyclase activators, and nitric oxide (NO) donors such as L-arginine. Many of these preclinical animal studies have reported promising results, but they remain experimental in clinical practice at this time.

Summary

Currently, most men with ED can be safely prescribed a trial of oral PDE-5 inhibitors following a basic history, physical exam, and basic laboratory studies. Patients with a contraindication for PDE-5 inhibitor use, or who have failed PDE-5 inhibitor use, may consider VED, intracavernosal/transurethral vasoactive therapy, or advance to surgical options.

Suggested reading

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