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ONE MINUTE CONSULT
BRIEF ANSWERS TO SPECIFIC CLINICAL QUESTIONS

Q: What are options for my patients with erectile dysfunction who have an unsatisfactory response to PDE5 inhibitors?

A 68-year-old man with diabetes, hypertension, and hyperlipidemia is experiencing unsatisfactory results with maximum doses of sildenafil (100 mg) and tadalafil (20 mg) for erectile dysfunction. You confirm he is taking his medication as directed. What are the next options for him?

A: Erectile dysfunction (ED), which affects 70% of men over 70 and more than 150 million men worldwide, is defined as a persistent inability to attain or sustain an erection suitable for sexual intercourse.[1] Phosphodiesterase type 5 (PDE5) inhibitors are first-line medical treatment for ED,[1] but up to 40% of patients do not have a satisfactory response to these agents.[2] Alternative therapies for patients who do not respond to PDE5 inhibitors or who experience intolerable side effects from them include intracavernosal injection, vacuum erection devices, and penile prosthesis implantation.

ED MANAGEMENT: GENERAL CONSIDERATIONS

Before medical therapy for ED is tried, it is crucial to address modifiable risk factors, counsel patients on lifestyle modifications, and identify any medications or underlying medical conditions contributing to ED. Risk factors for ED include smoking, obesity, cardiovascular disease, depression, prostate surgery, penile trauma, obstructive sleep apnea, and testosterone deficiency. Lifestyle adjustments such as weight loss, increased cardiovascular exercise, reduced alcohol intake, and quitting smoking can partially alleviate symptoms.[1]

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Also, a thorough history should explore psychological, psychosocial, and relational factors and sexual practices that may be impacting sexual performance, and referral to a sex therapist should be considered.

A diagnosis of ED can indicate the presence of systemic disease or reversible causes like medication side effects or testosterone deficiency (discussed below). When certain medications such as antidepressants or antihypertensives are suspected of contributing to ED,[3] the patient should be advised to talk with the prescribing physician to determine whether alternative medications with better side-effect profiles are available.

Beta-blockers are associated with ED, although the etiology is not well established.[4] Patient awareness or anxiety regarding ED as a potential side effect of beta-blockers may itself contribute to dissatisfaction with erectile function after starting a beta-blocker. While further study is needed, trying an alternative medication for patients on first-generation (propranolol) or second-generation (metoprolol, atenolol) beta-blockers may be considered. In a review of several small studies, Sharp and Gales[5] noted mildly improved or similar sexual function in patients after starting nebivolol, which was attributed to the beta-blocker's ability to stimulate endothelial release of nitric oxide, producing vasoactive effects and potentiating penile erection.

If feasible for the patient, medications like calcium channel blockers, angiotensin-converting enzyme inhibitors, or angiotensin receptor blockers can also be explored, as their risk for causing ED is thought to be lower. Thiazide diuretics at high doses have been associated with adverse effects on erectile function

compared with other antihypertensive drugs.[6] However, treatment of hypertension should remain the priority, and it may not be clinically appropriate to adjust antihypertensive medications, particularly without strong evidence to support the use of 1 medication over another.

The evidence regarding a correlation between statin medications and ED risk is conflicting. Some studies suggest that statins have sexual side effects, while others propose that the overall cardiovascular benefit of these medications contributes to improved erectile function.[7] No large-scale randomized controlled trials have established a link between statins and testosterone levels, and cessation of statin therapy or lowering of statin regimens as a means of improving ED is not recommended. Rather, we suggest optimizing well-established contributing factors such as cardiovascular fitness and testosterone levels.

PHOSPHODIESTERASE TYPE 5 INHIBITORS

Despite making lifestyle changes, many patients with ED require PDE5 inhibitors such as sildenafil or tadalafil to improve erectile function. These agents promote erections by increasing nitric oxide levels and blocking the decomposition of cyclic guanosine monophosphate, thereby relaxing the smooth muscle within the corpora cavernosa and increasing blood flow.[1] However, PDE5 inhibitors are efficacious in only 60% to 70% of patients.[2]

When starting PDE5 inhibitors, proper administration should be ensured, as a large proportion of treatment failures with these agents is attributed to incorrect use.[2] Sildenafil should be taken 30 to 60 minutes before intercourse on an empty stomach. The recommended window for taking on-demand tadalafil, which is not impacted by food intake, is 30 to 120 minutes before intercourse, but for optimal effectiveness, it should be taken 60 to 120 minutes before intercourse.[8] Daily low-dose tadalafil (5 mg) may be considered for men who also experience voiding dysfunction due to prostate enlargement or men with mild ED.

Patients taking 5-alpha-reductase inhibitors for benign prostatic hyperplasia who also experience ED and low libido should be referred to a urologist for alternative management strategies such as daily low-dose tadalafil, alpha-blockers, or minimally invasive surgical therapies. In fact, some selective alpha-blockers have been found to preserve or improve erectile function.[9] Combination therapy with daily tadalafil plus on-demand higher-dose tadalafil or sildenafil may be considered.[10]

Before determining that the medication has failed to achieve the desired result, several trials of PDE5 inhibitors with at least 24 hours between doses should be attempted.[11] Additionally, other reversible causes of ED, such as testosterone deficiency, should be assessed. An early morning testosterone level (before 11:00 AM) can identify testosterone deficiency in the presence of symptoms or signs of low testosterone such as low libido, fatigue, and loss of body hair.[10] Testosterone levels less than 300 ng/dL with these accompanying symptoms may warrant treatment with testosterone replacement therapy, which placebo-controlled randomized trials and meta-analyses have demonstrated may help improve erectile function and libido.[10–12] However, patients with ED but no symptoms of testosterone deficiency are less likely to benefit from replacement therapy. Assessment of testosterone deficiency is most valuable in men with borderline response to PDE5 inhibitors and with other signs and symptoms of low testosterone.

Once these avenues have been exhausted, exploring alternative therapies that aid in restoring erectile function should be considered.

OTHER THERAPEUTIC OPTIONS

Therapeutic options beyond PDE5 inhibitors include intracavernosal injection therapy, vacuum erection devices, and penile prostheses.[1,2,11] These alternatives are typically used when the patient does not respond to PDE5 inhibitors or experiences intolerable side effects (eg, headache, flushing, dyspepsia, visual disturbances, backache) from them. Treatment should be based on patient and partner preferences, comorbidities, and current medications.[2] The 2018 American Urological Association guideline on ED[11] emphasizes the importance of shared decision-making between patient and physician. In this process, the physician presents the various treatment options to the patient, and the risks and benefits of each are discussed before the treatment most aligned with patient goals and expectations is determined.

Intracavernosal injection

Intracavernosal injection is the direct injection of 1 or more vasoactive medications (eg, alprostadil, papaverine, or phentolamine) into the corpora cavernosa of the penis to promote an erection through local dilation of penile vessels.[11] Intracavernosal injection therapy is efficacious in providing erectile function adequate for sexual intercourse in 53.7% to 100% of patients.[11,13] However, it has higher long-term dropout rates, and its side effects include priapism, ecchymoses, hematoma, penile fibrosis, and penile deformity due to Peyronie disease.[14]

Vacuum erection devices

Vacuum erection devices induce erection by generating negative pressure, which enhances blood flow into the corpora cavernosa, and the erection is maintained with a constricting ring at the base of the penis.[15] Of note, despite initial use of vacuum erection devices for penile rehabilitation after prostatectomy, these devices have not been shown to definitively improve erectile function.[16] Side effects of vacuum erection devices are quite mild but may include discomfort, bruising, numbness, skin irritation, and pain from the constricting ring.[15] Vacuum erection devices are contraindicated in patients with coagulopathies or those taking anticoagulants.[17] Furthermore, combination treatment with PDE5 inhibitors and other accepted therapies such as vacuum erection devices may have greater efficacy than either as monotherapy.[18]

Inflatable penile prosthesis implantation

Another option for patients with ED refractory to more conservative therapies is surgical implantation of an inflatable penile prosthesis.[19] This option has the highest satisfaction rate, and is typically considered after failure of oral therapies in patients who do not desire injection or vacuum erection device therapy.[20] Inflatable penile prosthesis implantation can address penile deformity, making it a particularly advantageous option for patients with ED secondary to Peyronie disease, in whom intracavernosal injection therapy is contraindicated due to the risk of progressive penile scarring and deformity.[1]

Several different prostheses are available, including 2- or 3-piece inflatable penile prostheses or a malleable device.[21] Three-piece inflatable penile prostheses offer the most natural rigidity and flaccidity and are the most commonly implanted penile prostheses in the United States.[1]

Kucuk et al[21] found that patients who underwent inflatable penile prosthesis implantation had greater improvements in their International Index of Erectile Function score than patients who received tadalafil or intracavernosal injection therapy. Partner satisfaction also improved, as both patient and partner Erectile Dysfunction Inventory of Treatment Satisfaction scores were significantly higher with penile prostheses than with other treatment modalities. A multicenter study found that more than 90% of patients who received an inflatable penile prosthesis were able to engage in normal sexual activity following implantation.[22] Potential complications of penile prosthesis implantation include bleeding, infection, erosion, mechanical failure, need for revision surgery, and automatic inflation.[20]

SHOCKWAVE THERAPY

The mechanism of action of low-intensity extracorporeal shockwave therapy (Li-ESWT) in treating ED is unclear. It is hypothesized that extracorporeal shockwaves stimulate expression of endothelial nitric oxide synthase, vascular-endothelial growth factor, and other vascular growth factors, promoting vessel expansion and neovascularization that promote blood flow and erectile function.[23] The Sexual Medicine Society of North America regards Li-ESWT as promising but does not endorse its use beyond research given its novelty.[24] Since the release of this statement, further studies have demonstrated some efficacy of Li-ESWT in men with moderate ED, though an optimal protocol remains to be determined.[25]

It is important to differentiate between Li-ESWT and radial wave therapy, the latter of which uses low-pressure acoustic waves to deliver lower energy with less tissue penetrance compared with Li-ESWT.[26] Direct-to-consumer marketing from men's health clinics often use these 2 terms interchangeably even though a randomized controlled trial found no difference between radial wave therapy and sham therapy for treating ED.[26] The Sexual Medicine Society of North America corroborates this, drawing a distinction between Li-ESWT and radial wave therapy.[24] While regenerative therapies such as Li-ESWT in ED treatment require further investigation, patients should be informed regarding the lack of evidence to support radial wave therapy for ED treatment, particularly as radial wave therapy devices are often promoted as equivalent by health clinics for men.

WHAT NOT TO OFFER

Stem cell therapy was initially proposed to improve erectile function by promoting angiogenesis and tissue healing and reducing scarring, inflammation, and apoptosis.[27] Clinical trials have been limited, and its clinical application is still unknown. Similarly, platelet-rich plasma injections have been studied as an option for ED, but a recent randomized controlled trial found no difference in efficacy between platelet-rich plasma and placebo.[28] Thus, the Sexual Medicine Society of North America's position is that stem cell and platelet-rich plasma therapies should not be used in clinical practice.[24]

CONCLUSION

There are various effective treatment modalities for men who cannot tolerate PDE5 inhibitors or in whom these

agents fail. Treatment choice should take underlying comorbidities into account. Referral to a urologist experienced in sexual dysfunction can ensure that patients choose the option best aligned with their goals and expectations.

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