Chapter 39

Medical and Surgical Management of Erectile Dysfunction

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39.1 Introduction

Erectile dysfunction (ED) is defined as the inability to attain and/or maintain sufficient penile rigidity for sexual satisfaction. It is a complex, multifactorial condition that is part of the normal aging process, and thus most commonly affects middle-aged and elderly men. However, ED is seen in men of all ages, making it a common chief complaint in both primary care and urologic clinics. ED may result from several mechanisms: difficulty initiating erection (psychogenic, neurogenic, endocrinogenic), difficulty filling (arteriogenic), and/or difficulty maintaining blood flow (veno-occlusive) within the penis. This chapter will discuss medical and surgical management options for ED as well as psychosexual therapy, lifestyle modification, and hormone replacement therapy.

ED may be a manifestation of another condition and may resolve upon treatment of the underlying issue. In special cases including primary or predominantly psychogenic ED, poor overall health, or endocrinologic issues, specific management options are available and recommended.

39.1.1 Psychogenic ED

Most cases of ED involve a psychogenic component. Psychotherapy and psychosexual counseling are recommended in men with psychogenic ED as primary therapy or as an adjunct to organic ED treatment. Adjuvant psychosexual therapy may improve medical treatment efficacy [1] and adherence [2]. Counseling therapies assist patients and their partners with communication about sexual concerns, may reduce sexual anxiety, and allow discussion of strategies for integrating ED treatments into their sexual relationship.

39.1.2 Organic ED Secondary to Poor Overall Health

Lifestyle modification including changes to diet and exercise routines may have beneficial effects on erectile function in men with certain metabolic or cardiovascular comorbidities and may increase efficacy of ED treatments. Men with ED and metabolic or cardiovascular comorbidities have higher International Index of Erectile Function (IIEF) scores compared to counterparts who do not [3]. Smoking cessation may also lead to improved overall health and improvements in erectile function [4].

39.1.3 Organic ED Secondary to Hypogonadism

ED may present as a symptom of testosterone deficiency. While hormone replacement therapy alone is not an effective treatment for ED in these patients [5], testosterone-deficient men receiving combination hormone replacement and a phosphodiesterase type-5 (PDE5) inhibitor report better erectile function scores compared to men receiving either therapy alone [6]. Testosterone therapy in PDE5 inhibitor-nonresponsive patients results in improved erectile function [7], although testosterone monotherapy is not recommended in patients with normal testosterone levels. Optimum efficacy of PDE5 inhibitor medication is most likely to be achieved once testosterone levels are normalized [8].

39.2 Medical Management

Medical therapies for ED range from oral medications to locally acting agents to nonsurgical devices. We have already mentioned hormone replacement, a medical therapy useful in a specific population of men with ED, and will now discuss other significant medical ED therapies.

39.2.1 PDE5 Inhibitors

This class of oral medications remains the backbone of medical management for ED, and includes four FDA-approved agents – sildenafil, tadalafil, vardenafil, and avanafil – as well as several other PDE5 inhibitors approved for use in other countries. These medications assist with the arterial and venous mechanisms involved in erectile function, but notably do not affect the sexual arousal phase that relies on nervous input; they function by inhibiting the PDE5 enzyme, which breaks down cyclic guanosine monophosphate (cGMP). Inhibition of PDE5 results in elevated penile tissue cGMP concentrations, causing smooth muscle relaxation in the corpus cavernosum. Men receiving a PDE5 inhibitor should be educated regarding the need for sexual stimulation. Multiple medication trials may be required to establish efficacy, since medications differ in onset and duration of action. Men and partners should be counseled that initial non-response or inadequate response may be readily overcome with a dose increase just as adverse events may be ameliorated with a dose decrease. Treatment failure is largely attributable to incorrect use, and reeducation often leads to treatment success [9].

39.2.1.1 Use in the General ED Population

PDE5 inhibitor medications have been extensively studied in the general ED population, although the newer drug avanafil has been relatively less well-studied. PDE5 inhibitors appear to have similar efficacy in the general ED population, consistent across various measures of erectile function [3]. Differences in response rates between dose groups are small and usually not clinically significant. This is not true for many adverse events, which correlate directly with dose, supporting the recommendation that men use the lowest dose that produces acceptable outcomes. Dose titration and experimentation is a key step to optimize PDE5 inhibitor efficacy, so men may be offered dosing frequency changes [10] or an alternative PDE5 inhibitor [11]. Tadalafil is currently FDA-approved for daily dosing; all other PDE5 inhibitors were studied using on-demand dosing only.

39.2.1.2 Use in Special Populations

Not all PDE5 inhibitor have been evaluated in all special populations of men with ED (e.g., diabetes, benign prostatic hyperplasia [BPH]/lower urinary tract symptoms [LUTS], postprostatectomy, post spinal cord injury), but findings in general are similar to those reported in the general ED population, with data for avanafil generally limited [3]. For men with diabetes, sildenafil, tadalafil, and vardenafil appear equally effective. For men with BPH/LUTS and ED, sildenafil and tadalafil appear to have similar efficacy. For men with ED caused by radical prostatectomy (RP), efficacy also appears similar across the PDE5 inhibitors. For men post radiation therapy (RT) for prostate cancer, sildenafil and tadalafil appear to have similar efficacy. Dose-response effects in special populations have not been well-studied, but available data suggest that men with diabetes and men who are postprostatectomy have more severe ED at baseline and respond less robustly to PDE5 inhibitors; as a result, clinicians may consider initiating therapy at a higher dose.

39.2.1.3 Use in Post-RP/RT ED

Prostate cancer therapies including RP, RT, and systemic hormonal therapy may result in various degrees of ED, with the course of erectile function loss and recovery specific to the intervention. Post-RP ED involves either neuropraxia (temporary loss of nerve function) that may occur despite "nerve sparing," or complete nerve function loss following cavernous transection or removal. Concomitant penile vascular damage and cavernosal denervation also contribute [12]. Post-RT ED involves radiation-induced damage to the penile neurovascular supply [13]. Penile rehabilitation strategies following these treatments focus on sustaining and modulating nerve and vascular/cavernosal tissue function [14]. Due to their noninvasive nature and ease of administration, PDE5 inhibitors have been investigated most extensively for this purpose [15], although studies have yet to show a benefit over placebo in terms of restored erectile function. Lag time bias may be to blame; it is possible that a longer-term treatment schedule may be necessary to demonstrate erectile health recovery effects.

39.2.1.4 Contraindications

The clinician prescribing PDE5 inhibitors must be conversant with all potential disease state and medication contraindications. Nitrate medications taken with PDE5is can result in hypotension, so one medication should not be taken with the other prior to a washout period. Men using sublingual nitroglycerin for angina should not use this medication within 24 hours of PDE5 inhibitor use, or longer if using tadalafil, which has a longer half-life. Many other medications can also potentially interact with or influence the metabolism of PDE5 inhibitor, including antidepressants, antifungals, antihypertensives, and HIV/AIDS drugs [16]. PDE5 inhibitors should be used with caution in men with mild to moderate hepatic or renal impairment or men with spinal cord injury, given the potential for delayed metabolism; in men with severe renal or liver disease, use of PDE5 inhibitors is generally not recommended.

39.2.1.5 Adverse Events

Most adverse events associated with PDE5 inhibitor administration are mild to moderate, with dyspepsia, headache, flushing, back pain, nasal congestion, myalgia, visual disturbance, and dizziness most commonly reported. Rates of dyspepsia and dizziness were relatively similar across sildenafil, tadalafil, and vardenafil. Headache and flushing occur most commonly with sildenafil and vardenafil; back pain and myalgia with tadalafil; and nasal congestion with vardenafil. Sildenafil has the highest rates of visual disturbance [3]. Tadalafil is associated with lower rates of frequently reported adverse events – particularly headaches – due to daily dosing, which requires a lower dose compared to on-demand use, echoing the strong dose-response pattern seen in adverse events of PDE5 inhibitor therapy. Men post-RP and men post-RT reported substantially higher rates of adverse events than the general ED population; men post-RP reported higher rates in response to sildenafil in particular, while men post-RT reported higher rates across all PDE5 inhibitor as well as placebo groups. Men in this population may have heightened sensitivity to body sensations and/or increased needs for psychosocial support.

39.2.1.6 Other Concerns

Studies have suggested relationships between PDE5 inhibitor use and several conditions, notably nonarteritic anterior ischemic optic neuropathy [17], skin cancer [18], and prostate cancer recurrence [19], although the data supporting these conclusions is tenuous and contradicted by further investigation [20].

39.2.2 Local Therapies

Several locally acting options are available for assisted erection therapy. Intracavernosal injections (ICI) agents include alprostadil, or prostaglandin E1; papaverine, a nonspecific phosphodiesterase

inhibitor; phentolamine, an alpha-adrenergic antagonist; and atropine. In addition, alprostadil may be delivered by intraurethral (IU) and topical administrations as well.

39.2.2.1 Use of ICI

Men with contraindications to PDE5 inhibitors, who find them ineffective, or who prefer no oral medications in general may choose ICI. Of the available injectable substances, only alprostadil is FDA-approved in the USA and is the only medication typically used as a single agent. Combinations of medications, such as bi-mix (papaverine + phentolamine) or tri-mix (papaverine + phentolamine + alprostadil) are also used to improve efficacy via synergistic effects and side-effect reduction via lower dose of individual agents. Combination medications require pharmacy compounding since they are not FDA approved, which may present a barrier to treatment. ICI medications are effective and highly satisfactory in men from the general ED population as well as those with diabetes, cardiovascular risk factors, men who are postprostatectomy, and men with spinal cord injuries [3]. Men considering ICI therapy should have an in-office injection test to determine the appropriate dose and medication(s), to help them achieve confidence with the technique and to facilitate adherence. At this visit, the risks of priapism and the proper course of action should be thoroughly explained, such as attempting ejaculation followed by oral pseudoephedrine and application of an ice pack to the penis, if unsuccessful. If the erection nevertheless persists, the importance of obtaining timely urgent or emergent intervention should be emphasized.

39.2.2.2 Adverse Events Associated with ICI

Rates of successful intercourse are similar across medications and medication combinations, but adverse event profiles differ. Priapism, pain, and penile fibrosis or plaque formation are of particular concern. Priapism, defined as a prolonged erection that requires intervention in order to resolve, is most serious. The lowest rates of priapism occur with alprostadil monotherapy, although prolonged or painful erections are actually more common. Pain is, as can be expected, a common consequence of ICI, and can result from pain from injection, penile pain, genital pain, or a combination. Pain with injection most commonly occurs with papaverine monotherapy, while pain during erection is most associated with alprostadil monotherapy; pain overall is most associated with bi-mix. Penile fibrosis or plaque as well as other penile deformities have been reported with use of ICI, although no single medication or medication combination is clearly associated with higher risk.

39.2.2.3 Intraurethral Alprostadil

IU erectile medications are recommended for patients in whom PDE5 inhibitors are contraindicated or men or partners who prefer to avoid oral medication in general. Urination is recommended prior to administration (since residual urine aids in dissolution and dispersal), which consists of applicator insertion through the urethral meatus as the penis is held upright and pulled taut. Alprostadil is deposited by depressing a button on the applicator, which is moved slightly to separate the pellet from the tip and then removed. The penis is kept upright and rolled to improve medication absorption. ICI alprostadil has had higher success rates than IU [21], but requires needles, which may cause men to prefer IU administration. Chronic IU alprostadil has only truly been studied in men who had erections firm enough for intercourse in response to in-office testing. Combined with a relatively lower treatment success rate, IU should not be prescribed until a man has undergone instruction in the method, an initial dose-titration in the office, and detailed counseling regarding possible adverse events and actions to take in response. A large proportion of men who have a positive in-office test will not be successful in the home environment [22]. IU alprostadil comes with its own adverse events, most commonly genital pain, minor urethral trauma, urethral pain or burning, and dizziness. Episodes of hypotension or syncope are rare, and prolonged or painful erection is less common compared to ICI [23]. Priapism is not reported, but patients should nevertheless be instructed on safe responses and maneuvers.

39.2.2.4 Alprostadil – Topical

Alprostadil cream is an effective and well-tolerated alternative to conventional treatment of ED and is safe in men undergoing therapy with alpha-blockers, antihypertensive agents, and/or nitrates. It can serve as second-line therapy for patients who fail to respond to, or are intolerant of, oral PDE5 inhibitors, and for those in whom these agents are contraindicated or may cause drug–drug interactions [24]. The lack of interference with food and alcohol is another advantage, as it allows for a higher degree of sexual spontaneity [25]. Alprostadil topical cream is less invasive and has fewer side effects compared to its injectable counterparts, a benefit that addresses many issues encountered with currently available ED therapy and may decrease the relatively high discontinuation rate [26].

39.2.3 Devices

For men who wish to avoid medications altogether, vacuum erection devices (VEDs) serve as an effective and low-cost alternative and are associated with high patient and partner satisfaction rates [3]. A pump is placed over the penis and suction induced, which draws blood into the penis. A ring is then placed at the base of the penis to prevent venous outflow. Vacuum limiters reduce the risk of penile injury. Nearly all patients successfully use the device to have intercourse [27]. However, studies examining patient satisfaction and efficacy for VEDs were carried out prior to the availability of PDE5 inhibitor medications, and men may prefer PDE5 inhibitors if given the option [28].

39.3 Surgical Management

Surgical options for men with ED have variable rates of success and satisfaction. Penile prostheses (both malleable and

inflatable) have had great success, while vascular surgeries including arterial revascularization procedures and venous ligation surgery have significantly lower success rates.

39.3.1 Penile Prosthesis

Penile prosthesis implantation has been performed successfully in men from the general ED population as well as men from a variety of special populations [3]. Several devices are currently available, including malleable (noninflatable) models as well as two- or three-piece inflatable prostheses. Prostheses provide several advantages to medical therapy, including the ability to generate an erection on-demand for as long and as frequently desired. Potential risks and burdens include risks of infection, erosion, and device malfunction or failure. This treatment choice is essentially irreversible, since it is unlikely that a man's penis will be reliably responsive to other ED therapies after the prosthesis is removed.

39.3.1.1 Use of Penile Prostheses

Patients and partners generally prefer inflatable over malleable prostheses, depending on the specific model. Two-piece inflatable models are comprised of intracavernosal cylinders and a pump placed in the scrotum, whereas three-piece models add an intra-abdominal fluid reservoir. Two-piece models may be preferred for men in whom an abdominal reservoir may pose a risk (e.g., extensive scarring, kidney transplant) or those with poor manual dexterity. Malleable implants are more appropriate in certain situations including limited manual dexterity and cost concerns. A penile implant will not have a direct effect on libido; a man who is struggling with loss of libido should have this issue addressed separately. Although the penile implant will enhance shaft rigidity, it will not affect glans rigidity or enhance the processes of orgasm and ejaculation. Thorough explanation of the costs and benefits of each option are warranted, as more realistic preoperative expectations are associated with higher postoperative satisfaction [29]. Most adverse events are rarely serious and quickly resolve, such as penile edema or hematoma, corpus injury, urethral injury, acute urinary retention, and crura injury; postoperative pain usually resolves within three months. However, some adverse events are more serious and deserve further discussion, and include infection, erosion, and mechanical failure of the device.

39.3.1.2 Infection

Infection typically occurs within the first three months after surgery and usually requires removal of the prosthesis. Interestingly, there is no evidence currently that diabetic men are at higher risk of prosthesis infection than men from the general ED population [30]. Surgery should not be undertaken if there is evidence of systemic, cutaneous, or urinary tract infection. Perioperative antibiotic administration should include vancomycin or a first- or second-generation cephalosporin as well as an aminoglycoside before and after surgery. Use of antibiotic-coated prostheses [31] and the "no touch" technique reduce infection rates in the general ED population. "No touch" involves discarding all surgical instruments and changing all surgical gloves after the initial incision. Infected prostheses must be removed with antibiotic wash-out in the infected area. Systemic antibiotics are administered and the tissues allowed to heal. Once healing has occurred, a new prosthesis may be implanted; however, device placement may not be feasible due to scarring. If this occurs, penile shortening, change in penile shape, and loss of sensation are more likely. In men without evidence of sepsis or severe local infection, a new device may be placed immediately to avoid these complications. Antibiotic coatings appear to reduce infection rates during replacement [32].

39.3.1.3 Erosions

Erosion or cylinder extrusion occurs when the tissues at the tip of the penis are weakened, allowing the prosthetic cylinder to migrate into the head of the penis and through the skin, requiring surgical repair and reposition. Erosion rates are lower on average for inflatable models than for malleable models.

39.3.1.4 Mechanical Failure

Mechanical failure is more common with inflatable models and typically occurs when a component ruptures and leaks fluid. Refinements in design and materials have resulted in decreased failure rates; the majority of men will have a functioning prosthesis 10 years postsurgery [33]. More than half of mechanical failures involve pump malfunction followed by cylinder and reservoir malfunction. Device coating with parylene may protect against mechanical failure in certain models [34].

39.3.1.5 Managing Changes in Penile Length

Several strategies have been attempted to maximize penile length and girth after implant, including presurgical penile traction to maximize postoperative length [35], presurgical VED therapy to facilitate easier corporeal dilatation [36], or allowing longer cylinder placement at the time of surgery [37]. Preoperative VED use to soften corporeal fibrosis in men with a history of ischemic priapism or infection may facilitate successful implant of a device [38]. Several intra-operative techniques also have been examined, including ventral phalloplasty and suspensory ligament release [39]. Postoperatively, IU alprostadil [40] and PDE5 inhibitor medications [41] have been used to improve glans temperature, sensation, and enlargement. Successful penile dimension enhancement by using aggressive cylinder sizing and daily cylinder inflation postoperatively also has been reported [42]. There are insufficient data on specific approaches and techniques to constitute a reliable evidence base from which to provide clinical guidance regarding these approaches.

39.3.2 Vascular

Both arterial reconstruction and venous ligation surgeries have been attempted. Arterial reconstruction in certain candidates has had moderate success, but venous surgery has not been

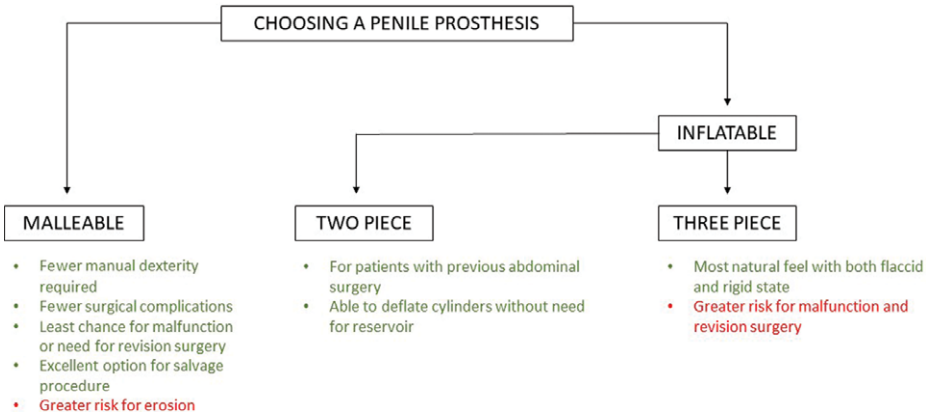

Figure 39.1 Benefits and costs associated with various options for penile prosthesis implantation

validated as an adequate treatment method even on those with solitary veno-occlusive ED.

39.3.2.1 Arterial

Penile arterial reconstruction surgery may be considered for the young man with ED without veno-occlusive dysfunction or evidence of generalized vascular disease or compromised vascular integrity. The long-term success of the procedure is not well established, although there is some evidence that surgery in ideal candidates leads to higher scores on erectile function questionnaires [43]. Patients respond well shortly after the procedure, but response rates decline over time. Predicting the long-term success of reconstructive surgery for a given man is extremely difficult, even in men without comorbidities and with good vascular health [44]. Frequently reported adverse events include penile hypervascularity, glans hyperemia, anastomosis occlusion, and postoperative edema or hematoma. Penile numbness, infection, shortening, bleeding, and inguinal hernia have also been reported.

39.3.2.2 Venous

Penile venous surgery is not recommended because of the lack of compelling evidence that it constitutes an effective ED management strategy in most men [3]. Even among men with pure veno-occlusive dysfunction, response rates vary over a wide range. Surgery is unlikely to result in long-term successful management of ED for the overwhelming majority of men and delays treatment with other more reliable options such as penile prosthesis surgery (Figure 39.1).

39.4 Future Direction and Experimental Therapy

Current therapies for ED are palliative in nature; future treatments are being developed that aim to restore erectile function rather than treat symptoms. However, treatments discussed in this section have not been studied sufficiently to be recommended for either general ED or special populations and should only be used in investigational settings.

39.4.1 Extracorporeal Shockwave Therapy

Low-intensity extracorporeal shockwave therapy functions by inducing cellular microtrauma, stimulating release of angiogenic factors that leads to neovascularization of the treated tissue [45]. The treatment's ability to restore normal erectile function is encouraging, but long-term duration of treatment effects is still being established [46]. Currently no serious adverse events have been reported.

39.4.2 Intracavernosal Stem Cell Therapy

Stem cell injection is well tolerated and appears to improve erectile function in men following radical prostatectomy [47] and diabetic ED [48] with no significant adverse reactions. However, the treatment's ability to restore normal erectile function in various populations of men with ED is still being investigated. Currently there are no randomized placebo-controlled trials assessing the efficacy of stem cells to treat erectile dysfunction. Long-term safety concerns include the risk of malignant degeneration, genomic or epigenetic changes, infection (especially with viral vector use), and potential immune reactions [49].

39.4.3 Platelet-Rich Plasma

Platelets play an important role in inflammation, tissue remodeling, and angiogenesis, leading to potential benefit of platelet-rich plasma (PRP) in vasculogenic ED. This treatment involves centrifugation of a blood sample to remove red and white blood cells and isolate platelets and plasma proteins in the supernatant, which is then injected into the corpus cavernosum [50]. Reliable information about potential benefits and risks/burdens of PRP therapy is not currently available.

39.5 Conclusion

ED is a multifactorial and complex condition affecting a wide range of male patients and is a common chief complaint in primary care and urologic clinics. A solid understanding of the many treatment options available will help physicians meet the needs of these patients.

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