
The medical and surgical treatment of erectile dysfunction: a review and update

Serkan Karakus, MD, Arthur L. Burnett, MD

The James Buchanan Brady Urological Institute and Department of Urology, The Johns Hopkins University School of Medicine, Baltimore, Maryland, USA

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Introduction: Erectile dysfunction (ED) is a common condition affecting more than 3 million men in the United States every year. Given the prevalence of severe comorbidities associated with ED, the clinician must take a thorough history and conduct a diagnostic exam accordingly. The clinician should consider that every man who presents with ED is unique with regards to his symptoms, degree of stress, associated health conditions, sexual relationship quality, and sociocultural context. The clinician determines an appropriate treatment plan that is aligned with the patient's and his partner's priorities and values, adopting a shared decision-making process. The clinician must possess sufficient knowledge of all available treatment modalities and be able to offer to all treatment options that are not contraindicated, regardless of invasiveness or irreversibility, as potential first-line treatments.

Materials and methods: Current medical and surgical treatment options in ED, including novel and innovative therapeutic options, were reviewed.

Results: There are a variety of treatment options for the management of ED, both medical and surgical. The most commonly considered medical treatment option is phosphodiesterase type 5 inhibitors (PDE5i), which has been proven successful in up to 65% of men with ED.

Other treatment options, such as vacuum erection device or intracavernosal injection therapy using vasodilator medications, should be considered in men who have contraindications or are non-responders to PDE5i. Surgical treatment of ED using penile implants has undergone multiple improvements over the years with low device failure and infection risks providing an effective and satisfying treatment alternative. Other therapies, such as penile vascular surgery, extracorporeal shock wave therapy, and intracavernosal stem cell therapies, are novel and should be considered investigational due to lack of evidence supporting their long term safety and efficacy.

Conclusions: The management of ED requires considerations of all aspects of the patient's health and involvement of the patient and his partner in the decision-making process. Patients should be informed of all available treatment options and be able to choose the option that is most aligned with their condition, goals, and risk tolerance. There are medical and surgical therapeutic options available in the management of ED, all supported with the best level of evidence. Novel therapeutic options are promising; however, randomized controlled trials with long term follow up periods and larger sample sizes are needed to support their safety and efficacy.

Key Words: sexual dysfunction, phosphodiesterase 5 inhibitors, vacuum erection device, intracavernosal injection, penile prosthesis

Introduction

Erectile dysfunction (ED) is not an uncommon condition that has a significant impact on the quality of life of men and their partners worldwide. Over 150 million men globally were affected by ED based on estimations in 1995, and this number is predicted to reach approximately 322 million by 2025.¹ The reason for the increase in the global prevalence of ED is believed

to be due to the increased prevalence of associated risk factors such as the global aging population, obesity, sedentary lifestyle, cardiovascular diseases, diabetes, depression, and BPH.²⁻⁴ ED prevalence is usually underestimated in many developing countries because help-seeking is rare among men with ED due to its associated stigma, and it is a non-life-threatening condition. However, previous research indicated that the presence of ED is a predictor of cardiovascular disease (CVD), dementia, and all-cause mortality.^{5,6} The most common underlying mechanism of ED is vascular, and symptoms of ED may precede a CVD event by up to 5 years, and the degree of ED correlates with the severity of CVD.⁷

Address correspondence to Dr. Arthur L. Burnett, The James Buchanan Brady Urological Institute, Johns Hopkins School of Medicine, 600 North Wolfe Street, Marburg 407, Baltimore, MD 21287-2101 USA

Given the high prevalence of ED and the high number of severe co-morbidities associated with it, the clinician must be able to conduct a valid diagnostic exam and offer available treatment options to patients. A guideline has been published by the American Urological Association (AUA) last updated in 2018 to provide a clinical strategy for the clinicians in the diagnosis and management of ED.⁸ Based on the AUA guideline for ED, men presenting with symptoms of ED should undergo a complete history and physical examination. Validated questionnaires such as the International Index of Erectile Function (IIEF), Erection Hardness Scale (EHS), and Sexual Health Inventory for Men (SHIM) are recommended to assess the severity of ED, to measure treatment effectiveness, and to guide future management. However, none of these questionnaires is valid for sexually inactive men. Laboratory tests such as fasting blood glucose, lipid profile, urinalysis, complete blood count, TSH, and serum testosterone can be done at the initial visit if the patient has an underlying condition.

Using the shared decision-making process as a cornerstone for care, all patients along with their partners, if possible, should be informed of all treatment modalities that are not contraindicated, regardless of invasiveness or irreversibility, as potential first-line treatments. For each treatment option, the clinician should ensure that the man and his partner have a full understanding of the benefits and risks/burdens associated with that choice. Additionally, the clinician needs to be aware of the health literacy of the patient, as well as social, cultural, religious factors.

Every man who presents with ED is unique based on his symptoms, degree of stress, associated health conditions, relationship quality, and sociocultural context. All treatment options that are not medically contraindicated should be considered; however, the clinician evaluating all these issues should determine an appropriate treatment that is aligned with the man and his partner's priorities and values. Additionally, ED occurs in a complex psychosocial context related to masculinity and sexuality. The patient should be strongly advised to receive psychotherapy or psychosexual counseling to promote treatment adherence, reduce performance anxiety, and integrate treatments into a sexual relationship.

This current article aims to conduct a review of current medical and surgical treatment options, as well as novel and innovative therapeutic options in ED.

Current treatment modalities for ED

ED has been significantly associated with general health status. Lifestyle modifications such as weight loss,

physical exercise, a healthy diet, smoking cessation, and reducing alcohol intake should be discussed with any man with ED. Lifestyle modifications show their effect via amelioration of endothelial dysfunction by inducing NO production, decrease in oxidative stress, reduced insulin resistance and lowering inflammatory state associated with metabolic diseases.⁹

In addition to lifestyle modifications, the AUA guideline acknowledges noninvasive and invasive treatment options, including oral phosphodiesterase type 5 inhibitors (PDE5i), vacuum erection devices (VED), intracavernosal injections (ICI), intraurethral suppositories, and penile prostheses for ED. PDE5i are usually suggested by clinicians as first-line therapy due to their clinical efficacies and safety profiles. However, any of these treatment options can be chosen as first-line therapy by patients.

Additional testing and specialist referral are typically options reserved for cases where initial treatments failed. Other indications for specialist referral include: (1) younger patients with a history of pelvic or perineal trauma, (2) patients with significant penile deformity, (3) complicated endocrinopathies, (4) complicated psychiatric or psychosexual disorders, (5) need for vascular or neurosurgical intervention, and (6) medicolegal reasons.

Novel approaches to treat ED, including but not limited to extracorporeal shock wave therapy (ESWT), penile vascular surgeries, stem cell therapies (SCT), and platelet-rich plasma (PRP), have shown promising initial results and may become more commonly suggested by clinicians for ED treatment.

Oral PDE5i

Oral PDE5i, including sildenafil, tadalafil, vardenafil, and avanafil, have been preferred as first-line therapy by clinicians due to their clinical efficacies and safety profiles. Up to 65 % of men who are taking PDE5i show a good response after initial treatment.^{10,11} However, the underlying pathophysiology of ED, such as post radical prostatectomy or radiation, and co-morbidities such as diabetes can decrease the success rate of PDE5i.¹²⁻¹⁵

Nitric oxide (NO) increases the cGMP levels in corpus cavernosum smooth muscle cells following reflexogenic or psychogenic stimulation resulting in penile erection by smooth muscle relaxation. PDE5i prevent cGMP degradation by inhibiting the PDE5 enzyme and keeping cGMP levels high.¹⁶ It is important to highlight that PDE5i are not effective without the induction of penile erection via NO release. PDE5i do not work sufficiently in diabetic neuropathy or cavernous nerve damage from pelvic surgeries, such

as radical prostatectomy or other pelvic surgeries, due to lack of neuronal NO release.

PDE5i are contraindicated in patients who are using nitrates due to leading potentially serious fall in systemic blood pressure. There is a possible drug-drug interaction between PDE5i and anti-hypertensive agents such as alpha-blockers or potent CYP3A inhibitors such as azole antifungals, antiretroviral protease inhibitors, macrolide antibiotics, and anti-depressants.¹⁷ The lowest possible starting dose should be prescribed, and the dosage should be titrated by close monitoring.¹⁸

Although PDE5i possess different biochemical and pharmacologic properties, all have similar efficacy in the general ED population. Sildenafil and vardenafil are similar with regards to the duration of action being up to 10-12 hours, with a peak absorption of 30-60 minutes. A high-fat meal decreases their efficacies, and the medication should be taken 1 hour before eating or 2 hours after eating to maximize absorption. Avanafil is absorbed in 15-30 minutes with a duration of action for up to 6 hours. The half-life of tadalafil is longer (17 hours), and its duration of action is up to about 24-36 hours with a longer onset of action of 60-120 minutes. Additionally, both avanafil and tadalafil are not affected by food intake. Tadalafil is the only oral medication approved by the U.S. Food and Drug Administration (FDA) to be used daily to treat ED, as well as to treat lower urinary tract symptoms in benign prostatic hyperplasia.

Dose titration of PDE5i is a key step to providing optimal efficacy while minimizing adverse effects. The man and his partner should be counseled with administration of an initial treatment dose, which may need to be decreased to alleviate unacceptable adverse effects or increased due to inadequate response. The variations in dose-response effects across PDE5i medications are small, non-linear, and generally not clinically significant. However, a clinical trial comparing dose-response effects of sildenafil 10, 25, and 50 mg reported variations on hardness, frequency and duration of erections, and frequency of sexual intercourse. Still, none of these alternative dosages altered the number of attempts at intercourse.¹⁹

When initiating treatment with PDE5i, the dosage can be chosen at mid-range; however, clinicians may consider initiating therapy at a higher dose for more severe ED when it is due to diabetes, radiation, or prostatectomy. On another note, penile rehabilitation with PDE5i remains unproven, and the early use of PDE5i following radical prostatectomy may not improve spontaneous unassisted erectile function.

If the patient shows symptoms and signs of testosterone deficiency with low total testosterone levels (< 300 ng/dL), PDE5i treatment for ED may require

combination therapy with testosterone to improve its effectiveness.^{20,21} Testosterone therapy is not sufficient for ED as a monotherapy; however, the restoration of testosterone levels likely supports the maximum efficacy of other ED treatment options.²² Most adverse effects associated with the use of PDE5i are mild to moderate, including dyspepsia, headache, flushing, back pain, nasal congestion, myalgia, visual disturbance, and dizziness.

Vacuum erection device

The VED is a mechanical device that is placed over the penis to generate a negative pressure to pull blood into the penis and cause an erection. A rubberized band is then placed around the base of the penis to maintain the erection during sexual intercourse. The device cost is low, and it is effective in men with ED associated with diabetes, spinal cord injury, post-prostatectomy, and other conditions. The satisfaction rate was reported up to 90%. However, the discontinuation rate was up to 30% due to pain and temporary changes to penile sensation due to the rubberized band, ejaculation problems, and bruising if the device is over pressurized.²³⁻²⁶ Additionally, its use may be difficult for patients with insufficient dexterity or a large amount of lower abdominal fat and buried penis.

Intraurethral alprostadil

Alprostadil is an exogenous form of prostaglandin E1 (PGE1). Alprostadil, in the form of a urethral suppository, is delivered into the corpus cavernosum by direct diffusion or via collateral vessels. As a result, intracellular levels of cyclic AMP increase in corpus cavernosum smooth muscle cells, leading to penile erection. This route of administration is less invasive but less effective than ICI. However, it may be a good option for patients who do not prefer injection methods or cannot use oral medication due to contraindications.²⁷ A test dose of medication should be administered in the clinic with patient to monitoring for hypotension and other possible adverse events such as penile pain and urethral burning. Additionally, instructions on the use of the urethral suppository can be given to the patient while titrating medication dose in the office.

Intracavernosal injection

A medication can directly be injected into the corpus cavernosum from the lateral base of the penis. Other injection sites are not preferable to avoid injecting the urethra in the ventral side and neurovascular bundle at the dorsal side. Papaverine, PGE1, and phentolamine are

commonly used injectable agents administered either as monotherapy or combination therapy in clinical practice. ICI is an alternative treatment for oral ED therapy with better satisfaction rates up to 94% and minimal systemic side effects.^{27,28} However, ICI therapy presents some barriers for patients or partners. Its administration is more challenging compared to other options. Also, it causes more anxiety due to the fear of injecting the penis. The first dose should be administered in the clinic to determine the optimal dosage to achieve a good erection that does not last longer than 1 hour. Additionally, a man and his partner may feel more confident with the method and facilitate adherence to the treatment after a self-injection training session.

The most commonly used medication for ICI is PGE1, also known as alprostadil, which is the only FDA approved medication to be used for ICI. The overall satisfaction rate of alprostadil monotherapy for ICI approximates 80% with dose titration from 1.25 to 20 µg.²⁹ Combination therapies are also recommended by clinical guidelines as an alternative to monotherapy to achieve higher efficacy and a more favorable side-effect profile by using lower dosages of each agent. Alprostadil can be combined with papaverine and phentolamine and called "tri-mix." When two medications are combined, it is called "bi-mix." A combination of papaverine and phentolamine is widely used as a bi-mix for injection even though it is not FDA approved for ICI in ED treatment. Papaverine is a nonspecific phosphodiesterase inhibitor and increases intracellular levels of both cAMP and cGMP. Phentolamine is an alpha-adrenergic receptor blocker and reduces sympathetic tone in the penis, thereby opposing vasoconstriction. Papaverine was the first medication discovered to be used for ICI. However, it is rarely used as monotherapy due to lower overall efficacy and higher AEs such as corporal fibrosis, high potential of priapism, and liver toxicity. Phentolamine also shows limited efficacy as a monotherapy. It is usually combined either with alprostadil or papaverine. Bi-mix utilizes the synergistic actions of cAMP elevation by alprostadil (20 µg/mL) with phosphodiesterase inhibition by papaverine (30 mg/mL) or alpha-adrenergic blockage by phentolamine (0.5 mg/mL), resulting in a response rate of 68.5%.³⁰ In combination with three mediations called tri-mix, and its overall success rate reported 72.6%.³¹ Concentrations of each component vary widely in the literature, but ratios of 12-30 mg papaverine: 10-20 µg alprostadil:1 mg phentolamine are common.⁸

Patients should be counseled regarding the potential AEs of ICI therapy. The most serious AE is priapism. Several studies reported a mean rate

of 6.3% for prolonged or painful erections and 1.8% for priapism using alprostadil, 8.9% for prolonged or painful erections and 5.5% for priapism using bi-mix (papaverine and phentolamine), and 2.8% for prolonged or painful erections and 3.1% for priapism using tri-mix.⁸ Penile and genital pain is one of the common AEs with bruising. The highest rates of pain have been reported in patients who were using either alprostadil or papaverine as a monotherapy. Additionally, penile fibrosis, plaques, and penile deformities have been reported with the use of ICI. Clinical guidelines suggested that clinicians should document the preexistence of any of these conditions before initiating ICI. Regular patient follow ups are essential for assessing the progression or onset of these conditions.

The contraindications of the use of ICIs include Peyronie's disease, a history of recurrent priapism, and bleeding disorders.

Penile prosthesis implantation

The penile prosthesis is a surgically implanted device that has been used for ED treatment over the last 40 years. The device has undergone multiple improvements over the years to minimize device failure and infection risk and optimize device function to maximize the patient's and his partner's satisfaction. There are a variety of forms of penile prostheses, including malleable and inflatable devices. The malleable device contains two semi-rigid cylinders that are implanted into the penile corpora. It is an ideal option for patients who are physically handicapped with poor hand dexterity. While malleable device has poor concealment, it has lower mechanical failure rates due to its minimal components.³² There are two types of implantable penile prosthesis (IPP) that consist of either two or three pieces. The two-piece IPP can provide full rigidity. However, the cylinders prefill with fluid due obviating the need for a reservoir, which achieves some degree of tumescence. It can be a good option for patients with the hostile pelvis. The three-piece inflatable penile prosthesis device consists of two fluid-filled cylinders that are implanted into the penile corpora, along with a pump that is placed in the scrotum and a fluid reservoir that is situated in the abdomen. It is considered a better option than the malleable prosthesis producing better penile rigidity and more flaccidity that closely replicates normal erection. The patient satisfaction rates of IPP are 86% that is higher than oral medication or ICI [guideline]. The 5 and 10 year overall survivals of modern prosthetics are estimated to be 90.4% and 86.6%, respectively.³³

Short term complications related to IPP implantation include bleeding, bruising, hematoma, wound separation, and severe pain, while long-term complications include erosion or cylinder extrusion, mechanical failure, and changes in penis length. Infection is the most serious AE, which may occur typically within the first 3 months or maybe as a late complication. It usually requires the removal of the prosthesis. However, infection rates have been reduced to 1%-2% after the development of antibiotic and hydrophilic coatings, as well as improvement in surgical techniques.³⁴ Penile prosthetic surgery should not be performed in the presence of systemic, cutaneous, or urinary tract infections.

The penile prosthesis may be considered as a first-line therapy; however, it is typically reserved for patients who have not responded to less-invasive ED treatments. Other ED treatments after prosthesis explantation generally are not successful. Given the invasive and essentially irreversible nature of penile prosthesis implantation surgery, thorough counseling regarding short and long term postoperative expectations (including possible penile length loss associated with ED) is essential.

Penile vascular surgery

Penile arterial reconstruction surgery may be considered for young patients who do not have any veno-occlusive dysfunction, evidence of generalized vascular disease, or other co-morbidities that could compromise vascular integrity.⁸ There have been numerous controversies due to the absence of large prospective and well-controlled studies. Also, the long term success of the procedure is not well-established.

Penile arterial reconstruction surgery would potentially be beneficial to an otherwise healthy patient aged < 55 years with arteriogenic ED. Occlusion of common penile or cavernosal arteries should be documented by penile duplex Doppler ultrasound or cavernosography and selective internal pudendal arteriography.

The surgical principle of penile arterial reconstruction surgery includes an anastomosis of the inferior epigastric artery to dorsal penile arteries in an end-to-side fashion or to the deep dorsal vein with additional proximal and/or distal vein ligation.³⁵

Penile venous ligation surgery is proposed to correct veno-occlusive ED; however, long term success is unlikely achievable for the management of ED.⁸ It is currently considered investigational due to inaccurate or deficient methods for diagnosing and correcting the relevant defect.

Extracorporeal shock wave therapy

Extracorporeal shock wave therapy (ESWT) on penile tissue is thought to be effective. due to microtrauma that upregulates the angiogenic growth factors and activates some factors for tissue restoration and repair. In addition to angiogenesis and tissue restoration, previous animal studies reported that ESWT improves erectile function in a rat model of cavernous nerve injury by inducing nerve generation via increasing brain-derived neurotrophic factor (BDNF) expression and neuronal nitric oxide synthase (nNOS)-positive nerves and activating Schwann cells.^{36,37}

ESWT has not been approved by the FDA and is still considered investigational. Several studies had reported its efficacy and safety in mild to moderate vasculogenic ED when PDE5i treatment failed.³⁸⁻⁴⁰ However, well-designed prospective randomized clinical trials are limited in the literature. The duration of treatment efficacy, optimal treatment parameters, such as dosing frequency, energy flux density settings, and the number of shocks, and the selection of device types (linear versus focused shock wave) are not well-established.

Randomized controlled studies with larger sample sizes are needed to determine its long term efficacy and side effects using a validated and standardized protocol.

Intracavernosal stem cell therapy

In recent years, there has been an increase in the use of SCT for ED treatment. Currently, mesenchymal stem cells isolated from adipose tissue are the most frequently used cells in studies. These stem cells are capable of differentiating into a variety of cells, such as cavernosal smooth muscle cells, endothelial cells, or neuron cells, that can promote cell growth and survival, angiogenesis, and immunomodulation via a variety of growth factors.⁴¹⁻⁴⁴ Previous animal studies using SCT have shown improvement in erectile function in diabetic ED, cavernosal nerve injury, and prostate radiation models.^{42,45,46}

There are several clinical trials in small study groups that have shown promising results using SCT without significant adverse effects in diabetic and post-prostatectomy ED.^{47,48} However, stem cells' differentiation capability as a progenitor cell presents safety concerns for the risk of malignant proliferation as well as potential immune response. In addition to these concerns, the long term efficacy of SCT is uncertain, as are the optimized source and dose of stem cells. Further randomized controlled studies are warranted with long-term follow up periods, standardized protocols, and larger study groups.

Platelet-rich plasma and other therapies

Platelet-rich plasma (PRP) is an autologous blood product that contains a high amount of platelets with various growth factors, including platelet-derived growth factor (PDGF), insulin-like growth factor (IGF), fibroblast growth factor (FGF) and vascular endothelial growth factor (VEGF). These growth factors have been shown to induce angiogenesis, cell regeneration, proliferation, and differentiation with stem cell migration in preclinical and clinical studies.⁴⁹⁻⁵³ Intracavernosal injection of PRP promotes nerve regeneration and the recovery of erectile function in rodent cavernous nerve injury models.⁵⁴⁻⁵⁶ However, there has been a lack of understanding of the underlying mechanism of PRP on neuroregeneration in studies using animal models of cavernous nerve injury.^{50,57,58}

A phase 1 human trial of intracavernosal PRP in 17 patients with ED and Peyronie's disease reported no major adverse effect. In the same study, ED symptoms

were assessed in 7 men using IIEF-5 questionnaire, and IIEF scores were found to improve by an average of 4 points while there was no decline in erectile function.⁵⁰ However, PRP is considered an experimental treatment, and higher-quality randomized controlled studies with larger patient samples with long term follow up are needed.

Conclusion

In clinical practice, the majority of patients with ED are placed on oral treatment with PDE5i as initial therapy. However, improving overall health with lifestyle modification and treatment of underlying comorbidities may alone enhance erectile function. The clinician should discuss all possible choices during the initial visit, regardless of its invasiveness, considering the patient's health literacy and sociocultural background. Shared decision making between clinician, patient, and partner plays a vital role in promoting treatment

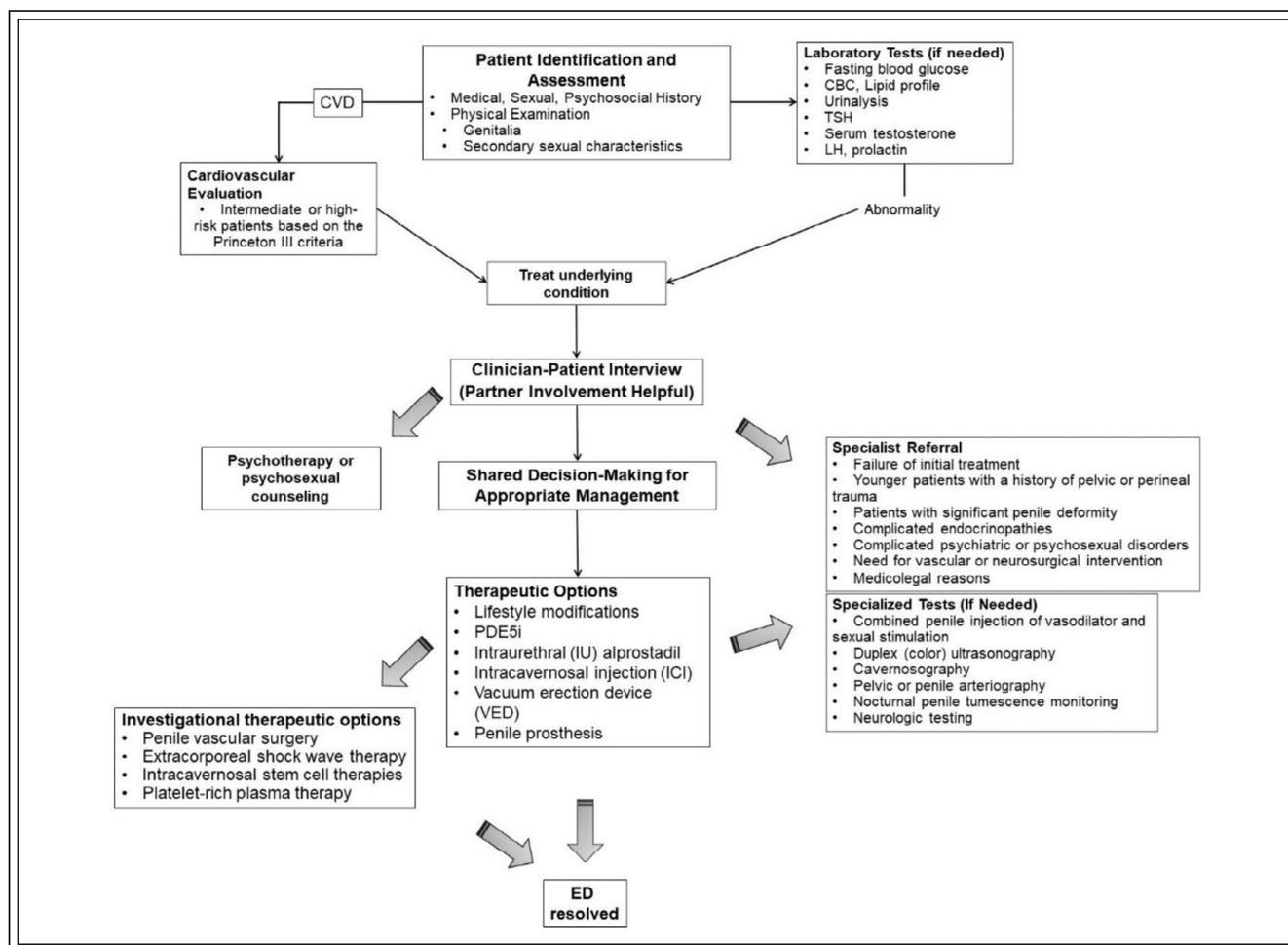


Figure 1. Algorithm for the management principles of patient presenting with erectile dysfunction.

adherence. Before starting PDE5i, the clinician should provide instructions to maximize benefits and efficacy. Dose titration is essential to achieve the best efficiency with minimal adverse events. Referral to mental health professionals should not be overlooked; performance anxiety and communication between partners need to be addressed to achieve full success.

Treatments such as transurethral alprostadil, ICI, or VED should be offered in case that PDE5i fails or there are contraindications to use of such medication. In-office injection tests should be utilized before initiating therapies like transurethral alprostadil or ICI to establish an effective dose and monitor adverse effects. In-office trials also help patients gain confidence with technique and facilitate adherence. If non-surgical options fail, penile prosthesis implantation should be discussed. The clinician should review the short and long term expectations of penile prosthesis implantation with the patient and his partner in-depth due to the irreversible consequence of surgery.

There have been many emerging therapies developed for ED treatment over the last decade. Some of these innovative and novel therapies, such as SCT, gene therapy, and PRP, may indeed replace or regenerate the endothelial, neuronal, and smooth muscle cells in the penis. However, the long term implications of these therapies are unknown. Well-designed randomized controlled studies adopting standardized protocols and including larger study populations are needed. An algorithm for the management principles of patient presenting with ED is described in Figure 1.

On another note, new pharmacologic agents targeting underlying pathophysiologies such as guanylate cyclase activators, NO donors, and RhoA/Rho-kinase inhibitors are promising therapies based on preclinical studies. Improvements in novel surgical techniques using tissue transplants and new device-based treatments such as novel drug or drug delivery systems may be implemented as ED therapies in the future.

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Dr. Serkan Karakus has no disclosures.

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