Erectile Dysfunction: Medical Treatment

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Summary

1. Lifestyle modifications including healthier diet, regular exercise, and smoking cessation can lead to improvements in erectile function and should be the first step in the treatment of erectile dysfunction (**Figure 1**).
2. Even after a previous phosphodiesterase type 5 inhibitor (PDE5i) failure, optimization with dosage and timing adjustments may lead to success.
3. Vacuum pumps, injections therapy and intraurethral suppositories remain viable options for treatment of erectile dysfunction. Proper expectations for each option should be discussed with the patient prior to initiating therapy.
4. Emerging technologies to treat erectile dysfunction are exciting areas of new research, but still have limited data regarding efficacy and/or durability.

Key Words

Erectile Dysfunction; Medical Treatment; Intracavernosal injection; Vacuum erection device; Phosphodiesterase type 5 inhibitors; PDE-5i; physical activity; diet; modifiable risk factors

1. Introduction

Optimal management of the man with erectile dysfunction (ED) requires a thorough assessment and understanding of erection physiology, vascular and neurological pathophysiology, patient expectations, patient social support, drug pharmacokinetics, drug costs and surgical techniques.

Evaluation of the man with ED is summarized in the AUA Core Curriculum section Erectile Dysfunction: Patient Evaluation, Investigations.

Once the decision has been made to treat a patient's ED, a shared decision-making framework should be used to identify appropriate treatment based on the values and priorities of a man and his partner (**Figure 1**). **Based on outcomes, adverse events, patient satisfaction, and partner satisfaction, treatment can be reassessed in a continuous cycle.**[1] A variety of treatments may be utilized until either the patient settles on a satisfactory treatment or he has exhausted all acceptable medical, surgical, and psychological treatment options. In cases of failure, counseling on adaptive

sexuality (e.g. finding new means for sexual intimacy and gratification) may be appropriate.

2. Lifestyle Modifications

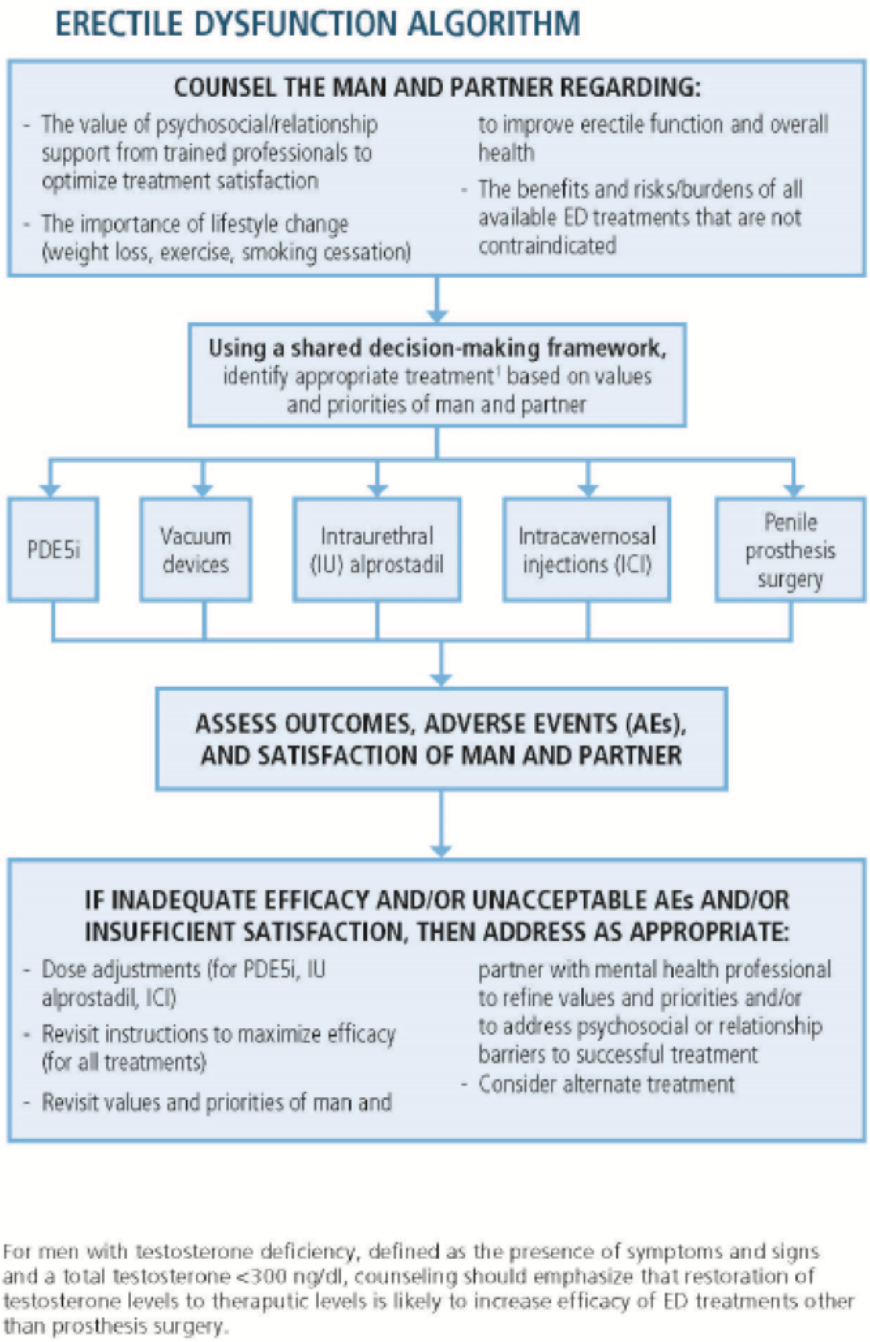

Figure 1: ED Algorithm, from Appendix A of AUA Guidelines on ED 2018, Appendix A.

Since ED is often a manifestation of generalized vascular disease, it makes sense in theory, and is demonstrated in practice, that lifestyle modifications that improve cardiovascular health may also improve erectile function.[2] When ED is identified, interventions to optimize the patient's cardiovascular health should be considered. Although numerous medications have been used to

manage vascular disease, lifestyle modification may decrease cardiovascular risk factors and empower patients to improve their overall health. **Eliminating**, **managing**, **or minimizing risk factors for cardiovascular disease may also improve erectile health and function**. Evidence from the Massachusetts Male Aging Study indicates that lifestyle changes are most effective for prevention/resolution of ED when they are started before age 50;[3] it may be hypothesized that lifestyle interventions in later life may be too late to reverse penile vascular disease.

2.1 Diet

There is growing international concern about the epidemic of obesity in developed nations; the prevalence of obesity continues to rise. Animal and human studies have demonstrated that obesity is a significant independent risk factor for ED. [4,5] Obesity may contribute to ED through a variety of mechanisms, including the presence of pro-inflammatory molecules (C-reactive protein, free radicals) and alterations of hormone levels such as testosterone deficiency (TD). Obesity and the metabolic syndrome (the combination of central obesity, insulin resistance, high blood pressure, and elevated lipids) are associated with many sexual problems, including ED and low sexual desire. [6,7]

Weight loss has been shown to produce significant improvements in erectile function amongst obese men. A series of studies from Italy have evaluated the relationship between diet and ED. Men on a Mediterranean diet (rich in polyunsaturated oils, fish, fresh produce and light in processed foods, saturated fats, dairy, and red meat) had lower rates of ED than those on a more typical Western diet.[8,9] More significantly, men enrolled in a two year program featuring a change to a Mediterranean diet from a Western diet coupled with advice for increased physical activity had improvement of ED as well as improvement in related risk factors (vascular function, decreasing pro-inflammatory molecules). Men who met progressively more of the study end-points (i.e. weight loss > 5%, fat intake reduced to less than 10% of energy consumed, fiber intake of 15 g or more per 1000 kcal, moderate exercise at least 30 minutes a day 5 days a week) were more likely to experience improved erectile function. This improvement was seen in all grades of ED from mild to severe.[10]

2.2 Exercise and Physical Activity

There is an inverse relationship between ED and physical activity. **Men who engage in regular vigorous physical activity have greatly reduced rates of ED.**[4,5,11] Physical activity is associated with reductions in vascular comorbidities known to be associated with ED risk (high blood pressure, glucose intolerance). However, physical activity appears to provide additional erectile function benefit not entirely explicable by modulation of these risk factors alone.[12] A recent meta-analysis showed increased physical activity led to a 3.85-point improvement in erectile function scores of the IIEF (95% CI 2.33 to 5.37).[13] Benefits of exercise are directly proportional to quantity of exercise and are independent of race.[14]

Additionally, exercise seems to increase the effectiveness of PDE-5is in treating ED. In a small pilot study, 60 patients with erectile dysfunction were randomized to either PDE-5i use alone vs. a

prescribed exercise and PDE-5i use. The mean energy expenditure in the exercise group was 1,868 kcal/week or 22.8 metabolic equivalents (MET)/week. The mean exercise time was 3.4 hours per week. All patients reported improvement in erectile function on PDE-5is, but there was a larger increase in the exercise group by 1.9 points in the erectile function subdomain of the IIEF. [15] Additionally, larger improvements in the confidence, desire, intercourse satisfaction, and overall satisfaction subscales of the IIEF were also noted. Similarly, several other studies have demonstrated improvement in erectile dysfunction in obese patients who lost weight.[16,17]

Overall, physical activity has been shown to help erectile function and may make treatments of erectile dysfunction more effective. Recommendation of physical activity to patients with erectile function has few downsides and may help both erectile function as well as overall cardiac health.

2.3 Medication Adjustment

Over 200 medications have been implicated in the pathogenesis of ED. **Anti-hypertensives have been clearly linked to ED**, **particularly non-specific beta-blockers and thiazide diuretics.**[11,18,19,20] Other common medications associated with ED include anti-androgens, anti-depressants (especially SSRI agents), and other psychotropics. When these medications are identified as a potentially significant contributor to ED, cessation should be considered if possible; if the medication is essential, substitution with a different agent in the same class may be worthwhile. However, robust evidence supporting the efficacy of medication adjustment is lacking. Changes in medications should be coordinated with the patient's prescribing health providers to minimize risk of discontinuing essential medications.

2.4 Tobacco and Alcohol Use

Multiple case controlled trials have demonstrated a dose-related association between tobacco use and ED.[17,21,22] Curiously, alcohol may have either positive or negative effects on erectile function, depending on how much is consumed. With smaller amounts (typically up to two normal volume beverages), there may be improved erection and libido likely due suppression of anxiety which may reduce anti-erectogenic sympathetic tone.[23] Increased amounts of alcohol are known to produce central nervous system sedation, decreased libido and transient ED. Chronic alcohol abuse may result in liver dysfunction, decreased testosterone and increased estrogen levels, and alcoholic polyneuropathy, all of which may affect erectile function negatively.

Habitual marijuana may contribute to sexual difficulties and has been linked to orgasmic function.[24] Other drugs of abuse (methamphetamine, opioids, cocaine) have also been associated with sexual difficulties.[25,26,27]

3. Over the Counter and Herbal Supplements

Supplements, nutriceuticals, and other over-the-counter (OTC) agents for ED have proven to be a robust industry, with minimal regulation. Common nutraceutical agents used for ED include dihydroepiandrosterone (DHEA), L-arginine, yohimbine, aveena sativa, terrestris tribulus and

ginsengs. **Data on the efficacy of herbal formulations for ED is variable and often of low quality.**[28] Despite the low quality of evidence, manufacturers may make claims of efficacy using carefully coded language that does not promise to treat or prevent a specific condition or disease.

There are several major issues to consider when addressing herbal medications with patients. The principal risk of OTC is an absence of regulatory oversight. Ingredients and dosages on OTC labeling may be incorrect or even absent. **There is also robust evidence that many OTC products are contaminated with approved or novel PDE5i**, **other medications**, **and even toxins such as heavy metals.**[29,30] For the nitrate-using patient, using such agents unknowingly consuming a PDE5i may be dangerous. Furthermore, some of these products contain androgens without clear labeling to this effect. Finally, the placebo response rates in ED drug trials is about 30%, thus much of any suggested benefit may be related to this placebo effect rather than to the agents within the formulation.

4. Phosphodiesterase Type 5 Inhibitors

The introduction of orally bioavailable pharmacotherapy for ED revolutionized sexual medicine and improved the lives of millions of men and their partners.[31,32] Selective inhibitors of phosphodiesterase type 5 (PDE5) have endured controversy,[33] as well as intermittent concerns about safety profile[32] yet have remained the standard of care therapy for ED.[34,35] PDE5i have demonstrated efficacy for ED of any etiology,[34] including psychogenic. In the context of psychogenic ED PDE5i may be best utilized in conjunction with psychosexual counseling.[36] PDE5i have also demonstrated utility across men of different racial groups, age, and health status although the degree of benefit may vary slightly based on demographic and health-related factors.[37]

In all studies published to date each PDE5i has demonstrated superior erectile response rate compared to placebo.[32,35] Typically success rates with first time prescription is 60-75%.[38,39,40,41] There is some heterogeneity in success rates as reported in the literature;[32] whether this represents a genuine difference in efficacy or is an artifact due to means of assessment or variability in patient population studied is unclear. It is clear that some men prefer one drug versus another; the rationale for preference may related to tolerability, efficacy, or economic concerns.[42] Longer-term studies have also shown good rates of sustained efficacy for PDE5i without tachyphylaxis.[35,43,44,45] **In addition to improvements in erectile function PDE5i have been linked to improvements in satisfaction with sexual life and partner sexual satisfaction.**[46,47,48]

4.1 History

The first commercially available PDE5i was sildenafil (Viagra®, Pfizer). This drug was initially developed for use as an anti-hypertensive and anti-anginal agent.[49] Sildenafil showed marginal efficacy for these indications but subsequent studies showed robust efficacy in the management of ED.[49] Sildenafil was brought to market in 1998.[31] Two additional PDE5i, vardenafil (Levitra®, GSK) and tadalafil (Cialis®, Lilly) were released in the United States in 2003. A fourth PDE5i, avanafil (Stendra®, Auxillium) was approved in 2013.[50] A variety of PDE5i have been developed outside of

the United States. Examples include lodenafil, mirodenafil, and udenafil.[32] PDE5is currently approved for use are summarized in **Table 1**.[35,51,52]

Table 1: Phosphodiesterase Type 5 Inhibitors				
Drug Name	**Trade Name**	**Tmax (hours)**	**Serum Half Life (hours)**	**Dosage (mg)**
Sildenafil	Viagra®, Revatio®	1	3 - 5	25-100
Vardenafil	Levitra®, Staxyn®	1	3 - 5	5-20
Tadalafil	Cialis®	2	18	5-20
Avanafil	Stendra™	0.5 - 1.5	~6	50-100
Lodenafil†	Helleva™	1.2	2	40-80
Mirodenafil†	Mvix™	1.125	2.5	50-100
Udenafil†	Zydena™	1 - 1.5	11 - 13	100-200
† Not currently commercially available in the United States				

4.2 Mechanism/Pharmacokinetics

PDE5 is the predominant phosphodiesterase enzyme in the penis.[53] PDE5 hydrolyzes cyclic guanosine monophosphate (cGMP) to the inactive form 1-prime guanosine monophosphate (GMP).[54,55] cGMP is a key regulator of calcium hemostasis and smooth muscle contraction in the penile vasculature; hence, depletion of cGMP by action of PDE5 will tend to oppose penile erection.[56] **PDE5i are competitive inhibitors of PDE5 by binding to the catalytic domain[54] and hence promote high levels of cGMP in the penile vasculature.**[35]

Due to the reliance of PDE5i on the presence of cGMP for efficacy, men with cavernous nerve injury or pathology (e.g. radical prostatectomy, diabetes) are less responsive to PDE5i due to upstream failure of the NO/cGMP pathway. **PDE5i have been shown to have less efficacy in men after radical pelvic surgery** (**estimated efficacy at promoting erections sufficient for completion of intercourse in 35-41%**)[57,58,59] **and/or autonomic neuropathy from diabetes**[35] (**estimated efficacy at promoting erections sufficient for completion of intercourse in 48-54% of men**).[51,56,60,61] Sildenafil and vardenafil are pyrazolopyrimidine compounds.[55] Peak absorption for each is approximately 30-60 minutes. The serum half-life of these drugs is 3-5 hours.[62,63] Tissue levels are likely to remain high after serum levels decline; this drives the observation that many men experience benefit from these drugs up to 12 hours after administration.[64]

Tadalafil is structurally distinct from vardenafil and sildenafil.[54] Peak absorption of this drug occurs between 2-4 hours with a half-life of 17.5 hours.[65] Tadalafil is the only PDE5i that is currently approved as a daily dose (as opposed to on-demand) treatment for ED.[66] Daily tadalafil has also demonstrated efficacy in the management of lower urinary tract symptoms from benign prostatic enlargement.[67]

Avanafil is an aminoheterocycle compound that is structurally distinct from other approved PDE5i.[68] Peak absorption occurs in 20-30 minutes and half-life is about 6 hours.[69]

4.3 Optimization of Use

A patient who presents to the urologist with “failure” of PDE5i should have a thorough evaluation of how the drug failed. Some men who receive PDE5i from a non-specialist do not receive instructions on the time and arousal requirements for maximal efficacy. It is recommended that men use the drug at maximum dose at least four times per acceptable protocol before declaring the drug a failure.

Because cGMP must be present for PDE5i to have any utility it is essential that PDE5i administration be coupled with sexual stimulation.[35] Up to 50% of PDE5i failures may be salvaged with re-education.[70] Some men who fail one PDE5i may have a better response to another. A trial of alternative PDE5i should be considered before advancing to other therapies.[41] Absorption of sildenafil and vardenafil is slowed by dietary lipids and hence they should not be taken after a meal, particularly one high in fat content.[53,62,63] Some authorities suggest ingestion of these agents in a pre-prandial fashion (1-2 hours prior to a meal). Tadalafil absorption is not impacted by food intake.[71] For men trialing sildenafil or vardenafil for the first time, it may be prudent to initially take these

medications on an empty stomach to determine maximal efficacy. Men should also be counseled that heavy alcohol consumption is an independent risk factor for ED and may increase the risk of side effects associated with PDE5i use. [72,73]

There is also evidence that men with testosterone deficiency have diminished response to PDE5i. Total testosterone less than 300 ng/dL is an independent risk factor for failure of PDE5i (odds ratio 1.89). [74] Supplementation with androgens may salvage some PDE5i failures in men with TD;[75,76] this should be contemplated in men who have signs and symptoms of testosterone deficiency coupled with failure of PDE5i.

Some authors have reported the use of PDE5i in excess of the United States Food and Drug Administration (FDA) approved dosing. In one non-randomized study, sildenafil at doses up to 200 mg on demand salvaged 13/54 (24%) prior non-responders to 100 mg dosing; this regimen had a markedly higher rate of side effects (63%) compared to standard dosing. Side effects led to discontinuation in 4 of the 13 responders (31%). [77] High dose PDE5i should be considered an off-label use of the drug and approached with caution; a detailed conversation with patients and about the increased potential for side effects and relatively low rate of success is required and should be documented before proceeding.

4.4 Contraindications

The only strict contraindication to use of PDE5i is concurrent use of nitrate containing medications (e.g. **sublingual nitroglycerin**, **isosorbide mononitrate or dinitrate**).[78] Concurrent use of nitrates and PDE5i may lead to a precipitous drop in blood pressure that may be life-threatening. While some clinicians allow men who do not use daily dose nitrates but who carry sublingual nitroglycerin to use PDE5i therapy, others feel uncomfortable with this scenario and insist that all nitrate containing medications to be discarded before PDE5i are prescribed. Recreational nitrite products, commonly referred to as “poppers”, contain chemical substances similar to amyl nitrite. These products are often packaged in small bottle similar to energy shot beverage products where they may be marketed as a sexual experience enhancement at online retailers and adult novelty stores. They may be labeled as a cleaning or deodorizing product to evade regulation. [79] Use these products may lead to hospitalization and or death, particularly when combined with other vasodilating agents such as PDE5i.[80]

PDE5i can also potentiate the hypotensive effect of alpha blockers. Patients on stable alpha-blocker therapy are advised to commence a PDE5i at one quarter maximum dose; dosage increases can be made as tolerated/indicated. Alpha blockers and PDE5i should be taken at least 4 hours apart from one another. Vardenafil is not recommended in men with congenital QT syndrome and men taking class IA or III antiarrhythmics (amiodarone, sotalol, quinidine).[78]

PDE5i are metabolized primarily by the cytochrome CYP3A4 system. While recommendations suggest that lower dosing and caution are advised in men who are using CYP3A inhibitors such as azole antifungals, protease inhibitors, and macrolides, such interactions may not be clinically insignificant depending on frequency of PDE5i dosing. Close monitoring of the patient for adverse

events remains essential.[78] Lower starting and maximum doses are recommended for men with hepatic failure.[81] Men with mild to moderate renal insufficiency do not require dosing adjustment with PDE5i; however, men with severe renal insufficiency (glomerular filtration less than 30 mL/min) should start at the lowest possible dose.[71,75,82]

4.5 Adverse Events

There is currently no data to suggest substantial differences in side effect profile between the currently available PDE5i.[32] Anecdotally, some men may report that a specific PDE5i is more side effect prone in their specific case. **The most common adverse events (AE) associated with this class of medications include headache, facial flushing, dyspepsia/heartburn, dizziness, nasal congestion, visual changes, and myalgia;**[32] the incidence of these effects ranges from 1-16% in most published series (**Table 2**).[83,35,84] The agents with the lowest incidence of visual disturbances are tadalafil and avanafil. The only agent with any significant association with myalgia (believed to be related to venous pooling within large skeletal muscle beds) is tadalafil.

Serious cardiac events have been reported after use of PDE5i; whether these events are related to the drug or to increased cardiac exertion during sex is unclear. However, there are over one hundred papers on PDE5i in the cardiology literature demonstrating their safety in properly selected patients. Adherence to the Princeton III guidelines maximizes the cardiac safety of PDE5i drugs.[85]

Priapism is a theoretical risk of any drug used for ED; however, the incidence of priapism with PDE5i is rare. A recent review of the United States Food and Drug Administration Adverse Reporting System Public Dashboard demonstrated that priapism was twice as common to be reported for second generation antipsychotics and trazodone than PDE5i. [86] Therefore, providers should be aware that the risk of priapism may be amplified in men with other predisposing conditions and/or who combine PDE5i with other drugs (prescription or recreational) that may have erectogenic effects.[87]

In the mid-2000s there was concern that PDE5i were associated with an increased risk of non-arteritic ischemic optic neuropathy (NAION), a cause of irreversible unilateral blindness. Analysis of existing data indicate that PDE5i may be associated with a slight increase in risk for NAION.[88] However, as the vascular risk factors for NAION are similar to ED and NAION itself is rare it is difficult to quantify the increase in risk of NAION with use of PDE5i; the absolute risk of NAION with or without PDE5i is very low.[83] In the original phase III trials, macular degeneration and retinitis pigmentosa were exclusion criteria and are therefore considered precautions regarding PDE5i use. Consultation with an ophthalmologist prior to use of PDE5i may be prudent if a patient has vision concerns.

PDE5i have been associated with auditory changes including tinnitus and temporary reduction in hearing; rare, yet uncorroborated post-marketing data have associated PDE5i with permanent hearing loss.[89,90] Although data linking PDE5i to permanent hearing loss are scant.[83] Men who experience decline in hearing or are concerned about this possibility should avoid use of PDE5i and

consider alternative therapies. [89]

Conflicting data have been reported on association between PDE5i use and biochemical recurrence after prostate cancer treatment. However, two recent large scale studies report that there is no association between PDE5i use and biochemical recurrence of prostate cancer after radical prostatectomy or external beam radiation therapy. [91,92] Data from a long-term trial of prostate cancer prevention reported no increased risk of prostate cancer (either low or high grade) in men using PDE5i; indeed, there was a trend (albeit an insignificant one, p=0.09) suggesting lower incidence of prostate cancer in men using PDE5i. [93,94]

There are also a number of observational studies linking PDE5i use with an increased risk of melanoma and basal cell carcinoma. [95] Meta analysis of 5 observational studies demonstrated an increased odds ratio of 1.12 (1.03-1.21 95%CI) for melanoma. [96] However, caution should used in interpreting these results. In the largest study to show increased risk of melanoma, there was increased risk with filling a single PDE5i prescription, but the risk was not elevated if more than one PDE5i prescription was filled. In addition, the group with melanoma had other predisposing factors to melanoma detection including higher educational level and higher income. As such, such associations should not be considered causative and more study is definitely needed in this area.

Table 2: Common side effects of PDE5I approved in the U.S.A.

	Sildenafil	Vardenafil	Tadalafil	Avanafil
Headache	15%	15%	14%	12%
Facial Flushing	14%	11%	4%	13%
Dyspepsia	6%	4%	10%	<1%
Rhinitis/Congestion	4%	10%	5%	4%
Back Pain	rare	rare	6%	3%
Myalgia	rare	rare	4%	rare
Vision Disturbance	5%	rare	0%	rare

5. Vacuum Erection Device

5.1 Description

The vacuum erection device (**VED**) **is a mechanical device used to generate a negative pressure environment around the penis to produce erection**. There are a variety of models available, ranging from simple cylinders with hand-driven pumps to complex electronic vacuum systems. Prescription VED are available for a variety of medical devices manufacturers; VED may also be purchased over the counter although such devices may be of low quality and typically do not possess a “pop-off” valve which limits the risk of over-pressurization.[97,98]

5.2 Mechanism of Action

These devices create a vacuum around the flaccid penis, which causes dilation of the cavernous spaces by negative pressure, drawing venous blood into the penis. The majority of VED are coupled with some form of constriction device at the base of the penis, which prevents venous outflow in order to produce and maintain an erection.

5.3 Optimization of Use

Although simple in concept, some patients struggle with the mechanical aspects of how to use the various types of devices available. **Dedicated training sessions will help optimize results**. Vendors often tout the superiority of specific vacuum devices and constrictive rings but "superiority" is more often driven by patient preference. Practice and a regular partner may optimize outcomes. Common patient concerns include:

i. inability to create a seal at the base of the penis; generally helped by trimming pubic hair and using adequate amounts of sealant (lubricating jelly).
ii. unstable penis related to the fulcrum effect at the point of placement of the constriction band – the penis is flaccid proximal to the band and rigid distal to it.
iii. penis looks and feels different to a natural erection – related to the retrograde venous filling of the subcutaneous veins and the corporal bodies leading to a bluish/grey coloration and coolness in the penis. Long-term compliance with the VED may be improved with coaching and provider advice.

5.4 Adverse Events/Side Effects

VED may lead to petechiae formation or hematoma if the device is over-pressurized. Ecchymosis or even skin necrosis may also occur at the site of the constriction band is left on for too long a time; recommendations are for band application for no longer than 30 minutes. [99] Depending on tightness of the ring disruption of ejaculation may occur; this may lead to pain with ejaculation, personal or partner distress, and potentially (although rarely) disruption of planned fertility. [99,100]

5.5 Contraindications/Precautions

Men taking anti-coagulants are at increased risk of bruising and/or petechiae. Men with a large suprapubic fat pad and subsequent buried penis may have difficulty operating the device. Men with a buried penis of other etiologies or those with a short penis may also experience problems with device operation. Men who do not have good manual dexterity may struggle placing the device or operating the pump; such men may benefit from electronic pumps. Men with penile deformity may find it difficult to use the straight tubular device.

5.6 Use in penile rehabilitation

One common use of vacuum erection devices is in the setting of post-prostatectomy penile rehabilitation, and often concomitantly with PDE5i. A recent meta-analysis of penile rehabilitation therapy showed improvements in overall erectile function and in those patients using PDE5i. [101] However, in this meta-analysis there were only 2 studies looking at use of VED only in the setting of penile rehabilitation. The first study showed that VED may have some potential benefit in stretching the tunica albuginea to prevent length. Early intervention with VED mitigated objective loss of length following radical prostatectomy, with a preserved penile length at 6 months (+0.6 cm) vs. loss of penile length (-1.8 cm) in those not utilizing a VED in the postoperative period. While men in the early intervention group saw improvements in mean IIEF at 3 and 6 months, there were no statistically significant differences between groups at last follow-up. [102] The other study found that daily VED use for 9 months postoperatively resulted in a smaller proportion of patient self-reporting subjective losses of penile girth and length compared to the control group (35% vs. 63%). In addition to subjective penile length, additional benefits of daily VED use included earlier ability to have intercourse and earlier return of natural erection sufficient for penetration, although final mean IIEF did not differ between groups. [103] Additionally, there may be value in implementing daily VED use for 1 month prior to penile prosthesis implantation. A recent randomized controlled trial demonstrated improved mean stretched penile length by 0.80 ± 0.38 cm and subjectively facilitated easier corporal dilation intraoperatively.[104]

6. Intra-urethral Suppository

6.1 Mechanism of Action

The Medicated Urethral System for Erections (**MUSE™**) **is an intraurethral suppository of prostaglandin-E_1** (**PGE_1**) **that is administered via the urethral meatus**. The suppository dissolves leading to PGE_1 diffusion across the urethra and into the corpus spongiosum and from there into the corpora cavernosa via collateral vessels. **PGE_1 increases intracellular levels of cAMP in smooth muscle cells.**[105,106,107] cAMP (like cGMP) is an intracellular second messenger which activates specific protein kinases leading eventually to a sequestration of intracellular calcium within the sarcoplasmic reticulum. Thus, calcium is less available to the cell leading to smooth muscle relaxation. By increased intracellular concentrations of cAMP and corporal and vascular smooth muscle relaxation PGE_1 leads to penile erection.

6.2 Optimization of Use

According to the 2019 AUA ED guideline, patients should undergo an initial administration and dose titration in the office prior to prescription for at home use.[1] **The main driver for this recommendation is to identify rare, but potentially life-threatening adverse reactions such as hypotension (should be given to administering the first dose of the agent in the office so as to monitor the patient for hypotension** (up to 3**% incidence at maximum dose**).[108] The patient should void immediately prior to administration for better dissolution of the tablet and absorption. MUSE™ comes in 125 mcg, 250 mcg, 500 mcg, and 1000 mcg doses. Many authorities suggest doses no lower than 500 mcg for efficacy in the treatment of ED. [109] Patients are advised to urinate prior to application. The penis is pulled straight out and up, and the applicator is placed into the urethra at which time the suppository is administered. The patient is recommended to remain standing and massage/stimulate the penis for up to 10 minutes to maximize absorption of the agent.

6.3 Efficacy

To date, two randomized-controlled trials and several comparative or observational studies have been published in the general population of men with ED who are treated with intraurethral alprostadil.[110,108,111,112] Success rates are highly variable, owing in part to the way in which success was defined by various study protocols. Specifically, many studies report success rates only amongst those who had a positive “in-office” response to the initial dosing.[1] This rate varies significantly across the available study protocols. In their randomized, double-blind, placebo-controlled trial, and the largest study to date to evaluate outcomes with intraurethral alprostadil, Padma-Nathan et al found that only two-thirds of men who received active treatment with dose-escalation of alprostadil had a sufficient response to in-office testing, defined as an erection sufficient for intercourse. [108] Of this group, only 65% of patients in the alprostadil arm were able to successfully complete intercourse on one or more occasions, suggesting that even amongst those in-office responders, many will not display consistent results at home. Mulhall et al found that only 34% of patients had a positive response in the office to intraurethral suppository, and of those, only 31% were continuing to use intraurethral therapy at 9 months follow-up with good response. [112] Importantly, intraurethral alprostadil is generally considered less efficacious compared with intracavernosal injections (discussed below), based on multiple comparative studies.[110,113] Combination intraurethral alprostadil and PDE5i’s may offer greater efficacy and “salvage” some patients who are non-responders to monotherapy. [114]

6.4 Adverse Events/Side Effects

Based on data from the two randomized-controlled trials (n=486 patients), side effects with intraurethral alprostadil are relatively frequently but usually mild and self-limited.[108,111] **Penile pain was the most common, reported in 36% of patients. Urethral burning was seen in 12% of patients, while mild urethral bleeding/spotting or testicular pain were reported in 5% of patients.** Also, 6% of female sexual partners reported vaginal burning/itching compared to 1% in a matched placebo group. Priapism is possible with MUSE™ but the incidence appears to be low, and

no episodes of priapism or penile fibrosis were reported in the two randomized-controlled trials.[108,111] Rarely (~2% of uses) patients may experience dizziness, presumably from hypotension due to systemic absorption of the PGE_1.

6.5 Contraindications/Precautions

MUSE™ is contraindicated in patients with a known hypersensitivity to PGE_1. Additionally, patients with structural abnormalities of the urethra such as urethral stricture, balanitis, urethritis, or severe hypospadias are recommended to proceed with caution when using MUSE™. Patients with sickle cell anemia or trait, thrombocytopenia, polycythemia and multiple myeloma (which all increase the risk of priapism) should also use MUSE™ cautiously. **Finally**, **it is recommended to not use during sexual activity with a pregnant female partner unless a condom is used due to concerns about transfer of prostaglandin and potential induction of labor**.

6.6 Alternatives

PGE1 administered alone or in combination with other erectogenic agents as an intra-urethral gel are available through compounding pharmacies. There is growing interest in these and other forms of topical applications of erectogenic medications. However, there is little published literature on the safety and efficacy of these therapies, and further study is needed.[115,116] As such, these therapies are not currently recommended by the AUA ED guideline panel.[1]

7. Intracavernosal Injection Therapy

7.1 Mechanism of Action

Intracavernosal injections (ICI) **involves the process of injecting a vasoactive agent** (**or combination of agents**) **directly into the corpora cavernosa**. This results in penile erection by relaxation of vascular smooth muscle and increased arterial flow into the penis. It is typically possible to perform this injection via a 29-31 gauge needle so the discomfort from the needle itself tends to be minimal.

ICI as a means to treat ED was introduced in 1982 (see **Table 3**).[117,118] **The single-agent most commonly used is PGE_1 (alprostadil), which is a direct cAMP stimulator**. Use of PGE_1 as monotherapy by penile injection is FDA-approved (Caverject™, Edex™). Two other agents, papaverine and phentolamine, are commonly utilized in erectogenic therapy most frequently in combination with each other and/or PGE_1. These agents are not FDA approved for this indication but are widely used. **Papaverine is a non-specific phosphodiesterase inhibitor and increases intracellular levels of both cAMP and cGMP**.[119] Papaverine can be used as monotherapy, or in combination.[120] **Phenotolamine is an alpha-1 adrenergic receptor blocker which reduces sympathetic tone in the penis**, thereby opposing vasoconstriction.[119] Phentolamine inhibits **detumescence** rather than directly promoting **erection**, and as such is only used in combination with alprostadil and/or papaverine. Compounds that contain two of these three erectogenic agents (most commonly papaverine and phentolamine) are commonly called “bimix” whereas compounds

containing all three of the above agents are called “trimix.” **It is important to note that there is no standard formulation of bimix or trimix;** each compounding pharmacy may produce a solution that differs markedly in concentrations so it is essential to be familiar with the specific content of a given solution. **A detailed synopsis of studies on ICI is available for review in Table 4.**[121,122,123,124,125,126,127] **Studies comparing ICI to other treatments is available for review in Table 5.**[110,113,128]

Table 3: Intracavernosal injections

Drug Name	Trade Name	Mechanism of action	Common side effects
Alprostadil (PGE_1) †	Edex®, Caverject ®	Increases intracellular cAMP via stimulation of Adenylate cyclase receptor	Penile pain (25%) Priapism Dizziness / hypotension (rare) Fibrosis (rare)
Papaverine	N/A	Non-specific phosphodiesterase inhibitor results in higher intracellular levels of cAMP and cGMP	Penile pain Fibrosis Priapism Hypotension
Phentolamine	N/A	Direct alpha-1 receptor agonist results in pathway leading to increased smooth muscle intracellular calcium (i.e. vasoconstriction)	Priapism Dizziness / hypotension Fibrosis

† FDA approved for the treatment of ED

7.2 Optimization of Use

No matter what formulation is chosen for injection therapy, it is prudent to give a low test-dose in the office under the supervision of a medical practitioner.[126] This permits education of the patient on technique and safety as well as defining a safe dose for the patient to use in the at-home setting. Some practitioners insist on two office visits for training. Men who experience a prolonged erection in the office setting can be treated with an intracavernosal injection of an adrenergic agent (most commonly phenylephrine).[129] However, it should be noted that some patients fail to achieve an erection quality erection during in-office test dosing. These patients should be instructed on safe practices for slow up-titration at home, and should also be counseled on potential risks for priapism and pertinent avoidance/management strategies.[1]

Medications should be administered directly into the corpus cavernosum. It is not necessary to inject both sides as there are fenestrations along the midline corporal septum that along diffusion of the medication between corporal bodies. The dorso-lateral portion of the base-middle of the penis is the ideal injection site. Direct dorsal or ventral injection should be avoided to minimize risk of injury to the neurovascular structures or urethra respectively. Men should be advised to alternate the site of injection and to avoid superficial blood vessels. A low dose should be utilized for the initial injection; dosage can then be titrated under the guidance of a clinician until the desired erectile effect is achieved. Some practitioners combine this initial office injection with penile duplex Doppler ultrasound to facilitate dose and strength titration.[130] Moreover, concurrent penile duplex Doppler ultrasound can identify patients with severe venous leak who may be refractory to ICI and should thus be considered better candidates for concurrent penile construction band or penile prosthesis placement. ICI should be used no more than once every 24 hours and no more than 3 days a week. However, this recommendation is somewhat arbitrary but is suggested to reduce the likelihood of priapism, fibrotic reactions, and/or Peyronie's Disease from multiple injections.

The main barrier to this therapy is fear of penile injections.[127] Frequent injection leads to better acceptance. Dose titration is often necessary for optimal effect; standardized patient education and close consultation with the prescribing provider is recommended when dose titration is contemplated.

7.3 Efficacy

ICI is highly effective at helping patients with ED achieve an erection. The 2018 AUA ED guideline panel performed an extensive review of the available literature.[1] They found that, based on the population and study protocol 54-100% of patients were able to achieve erection rigidity satisfactory for penetration. There was also no obvious different amongst the various medication combinations with respect to efficacy. The strength of the evidence is limited, as most studies were observational (i.e. weakest level of evidence). In the first rigorous trial to evaluate treatment efficacy, authors from the Alprostadil Study Group carried out a series of three different studies at 51 international sites. [121] When alprostadil was administered in the office, roughly 50% of patients achieved a clinical response, defined as >70% penile rigidity as determined by the evaluating physician. In contrast, no

patient achieved a response when placebo was injected. Furthermore, in the open-label phase of the study, which involved 471 patients who administered alprostadil at home, 87% of the total injections administered resulted in satisfactory sexual intercourse based on patient report.

Treatment success can also be defined by patient satisfaction. Based on the AUA ED guideline panel's review, patient satisfaction in the published literature varies from 46 to 99%, with papaverine monotherapy showing the lowest mean satisfaction rates.[1] A substantial number of men who start on penile injection therapy will discontinue. A cohort study in 368 men after prostate cancer surgery indicated that 140 (38%) had used penile injections but just 34 (24% of the 140) were using injections at eight year follow up. [131] Older age, younger partner age, and fully rigid erections (i.e. therapeutic efficacy) are associated with increased satisfaction.[126]

7.4 Adverse Events/Side Effects

Side effects with ICI are common, but tend to be self-limited.[1] The most common side effect is penile pain. Up to 50% of men using single agent alprostadil will report penile pain although the degree of associated bother may be variable. [121] The incidence of penile pain may decrease with use of a lower dose of alprostadil or removal of the alprostadil entirely by substitution using compounded mixtures. In addition, roughly 3-5% of men will report nodularity on the penis. ICI therapy may cause bruising and ecchymosis (~25%), which can be minimized by alternating injection sites and holding pressure post-injection. Less frequently, a hematoma may form after injection, which is thought to result from injury to a superficial penile vein. Gentle compression for a few minutes after each injection is suggested to minimize the risk for ecchymosis and hematoma. Headache and dizziness have been reported by about 1% of patients using ICI. [121] As a result of either treatment related side effects or lack of efficacy, a significant portion of patients will discontinue therapy within the first few years.

The most serious adverse event of ICI is priapism. In studies evaluating the safety of alprostadil, true priapism was reported in 0-10% of patients, with an average rate of roughly 1.8% of the study populations.[1] The rate of "prolonged painful erection" was somewhat higher, with an average rate of 6% (range 0-43%). The highest rates of priapism seem to occur with intracavernosal papaverine (average 7%), and are slightly lower for bimix (average 5.5%) and trimix (average 3.2%) depending on the study population and medication concentrations. The goal with ICI is to achieve satisfactory erection rigidity sufficient for intercourse, typically for 30-60 minutes but not to exceed two hours. If a patient has sustained erection rigidity in excess of two hours, frequently utilized strategies including ejaculation, oral pseudoephedrine, and applying ice to the erect penis. It is important to note that these recommendations are based in large part on anecdote, and patients must be instructed that urgent/emergent medical evaluation is necessary if a rigid/painful erection persists, particularly if the duration is approach 4-6 hours.[1] Injection of an adrenergic agent (most commonly phenylephrine) can be given intracavernosally.[132] If there is not adequate detumescence after adrenergic agonist injection, corporal aspiration with or without irrigation with dilute adrenergic agent solution should be performed. If the priapism persists, then surgical shunts may be necessary. Priapism can be prevented by education and close monitoring of patient, which underscores the AUA ED guideline

panel's recommendation to perform an in-office injection test at the start of ICI therapy. Please see the **AUA/SMSNA Guideline on Acute Ischemic Priapism** and the AUA Core Curriculum **Consults & Emergencies: Priapism** chapter for more information.

7.5 Contraindications/Precautions

There are several important patient-specific factors that should be taken into consideration before prescribing ICI.[133] Injection anxiety levels decrease over time, but overall remain high. Nelson et al found that more than 40% of men performing ICI for ED after radical pelvic surgery continued to report "high" injection-associated anxiety four months after starting treatment.[127] Men who are unable to tolerate needles and those who are unable to perform the injection procedure (and where partner is not able to or unwilling to inject) should not be prescribed ICI therapy. Patients with a short or buried penis, large pannus, poor vision and poor manual dexterity may be better off having a partner (if available) perform the injection. Patients with known hypersensitivity to any of the injected agent(s) should avoid ICI. In addition, patients with an increased risk of developing priapism (sickle cell anemia, leukemia, or multiple myeloma) or a history of priapism should only use ICI therapy under the closest of supervision. The safety of ICI in these populations has not been well-studied. Similarly patients with Peyronie's disease should be carefully monitored if using ICI given the theoretical risk that ICI may encourage tunical fibrosis, thereby exacerbating penile deformity.

Monoamine oxidase inhibitor (MAOI) medications are a contraindication to the use of alpha adrenergic medications (phenylephrine, epinephrine), so patients on MAOI agents should be prescribed ICI with extreme caution.[134] Patient using mild anti-coagulants can use ICI as long as close attention is paid to compression on the injection point for several minutes after the narrow gauge needle is removed; however, these patients are at increased risk of bruising and/or hematoma formation.[135]

8. Combination Therapy

Combination therapy has been suggested as a treatment option for some men with ED that does not respond to single modality treatment.[136] This approach may be effective in some cases but has been associated with increased risk for adverse events including priapism.[137]

A study of 34 radical prostatectomy patients indicated that over two-thirds experienced enhancement of their response to maximum dose PDE5i after addition of ICI with PGE_1.[138] A larger study in 93 men who had previously failed management with ICI demonstrated better response when sildenafil was added to ICI; a higher rate of side effects (penile pain, flushing, headache, and dizziness) was reported in this study in men using combined therapy compared to men on sildenafil alone.[137]

Combination of PDE5i with intraurethral prostaglandin suppository (MUSE™) was used in a study of 28 men who had failed either agent as a monotherapy at maximum dosing.[114] The authors reported "reproducible results" in all 28 patients with all patients reporting that this treatment improved their erections. A similar study focusing entirely on prostatectomy patients reported enhancement of erectile function in 19/23 men (83%) who had previously failed maximum dose sildenafil. Patients in

the successful cohort reported ability to obtain erection sufficient for penetration a mean of 80% of the time. [138] Combination therapy for ED should be considered off-label use and approached with caution and meticulous patient education on safety protocols. Documentation of this conversation and patient understanding in the medical record is essential.

9. Adaptation of Sexual Activity

While erectile function is important for men and their partners, it is only one component of a healthy sexual relationship. Some couples may not be candidates for ED therapy or may reject medications/surgeries for sexual concerns. Since erectile rigidity is not necessary for tactile sensation, orgasm, and even ejaculation some couples may elect to omit penetrative intercourse and pursue “sexual outercourse”. Sex therapists or other professional counselors may be very helpful in educating couples about alternatives to penetrative sexual relations.

10. Investigational or Experimental Therapies

Many men consider the medical and surgical interventions for ED to be “unnatural” and request regenerative therapies. As discussed above, life-style changes should always be encouraged for optimized vascular and endothelial function. Due to this interest in “restorative” or “regenerative” therapies, various therapies have been touted, albeit without robust supporting data, such as low-intensity shock wave therapy (LiSWT), stem cell therapy (SCT), platelet-enriched plasma (PRP). [1] At this time, there is no FDA approval of any of these alternative therapies. Given the lack of clear efficacy, these **alternative therapies** are still considered either investigational or experimental by the AUA and the Sexual Medicine Society of North America (SMSNA). Readers are specifically referred to the SMSNA position statement on restorative therapies for ED for a detailed review and synthesis of the available evidence. [139]

There has been great interest in recent years on LiSWT for management of ED. Preliminary findings in several randomized, controlled trials appear encouraging in terms of shock wave therapy’s potential to improve erectile function and responsiveness to medical therapies for ED.[140] [141,142,143] In preclinical studies, LiSWT demonstrates a multi-modal mechanism of action, including angiogenesis and recruitment of stem cells. While short term benefits are frequently described, durability beyond the initial few months has not been adequately studied . [144,145,146,147,148,149] Additionally, the LiSWT studies consist of highly variable protocols in terms of the type of shockwave used (i.e. linear versus radial), treatment parameters (frequency and amount of energy delivered, shockwave machine settings, etc.) and defining the treatment population. LiSWT seems to be very safe, with few to no adverse events. Overall, shock wave therapy should not be considered a primary treatment for ED outside of a clinical trial setting at this time. [1]

SCT has attracted a great deal of interest for a number of medical conditions, including ED. SCT also seems to function in a multimodal manner, via various mechanisms including angiogenesis and growth factor release.[150] A number of studies in animal models have reported favorable pre-clinical results.[138] While there is great potential for stem cell therapy it is not recommended for management

of ED outside of a clinical trial setting at this time. [1]

Finally, platelet-rich plasma (PRP) injection has also being investigated as a potential treatment for ED. As with the other alternative treatments, PRP is used in a wide variety of medical conditions and works via providing a high concentration of growth factors and activated platelets. [150] Overall, there is little peer-reviewed data on this treatment.[151] However, Poulious et al recently published the results of the first randomized, double-blinded, placebo controlled trial looking at short term (3 month) outcomes with PRP for ED. [152] The authors found that a minimal clinically important difference in ED based on the international index of erectile function scores was achieved in 69% of the patients in the PRP group compared with only 27% of patients in the placebo group. The mean change in IIEF-Erectile function domain score was 3.9 points. Despite these promising early results, experts do not recommend that PRP is used outside of a clinical trial setting at this point. [1,139]

11. Conclusions

A host of medical treatment options are available for men with ED. Therapy for ED should start with the least invasive option; escalation of therapy may continue until satisfactory results are obtained. If medical options fail, alternative sexual practices or surgical intervention should be considered.

12. Additional Tables

Table 4: Studies on Intracavernosal Injections for ED

First Author	Design	Study Arms	Efficacy and Other Outcomes
Linet 1996[121]	Prospective cohort study	- Summary data of three separate studies - Open-label flexible dose study of home ICI including: - 683 men - 33 sites	- 577 men - 13,762 injections - 82% of injections resulted in satisfactory sexual activity.
Sundaram 1997[122]	Retrospective survey	- Questionnaires were mailed to 108 men who used ICI for 5 years or more.	- 32% of patients were still on ICI at follow-up - Most men discontinued used in the first year. - 82% of patients would still recommend ICI to a friend.
Porst 1998[123]	Prospective cohort study	- 162 patients who were enrolled in a European ICI program at 3 sites. - Patients were followed for up to 4 years.	- Overall, over 90% chance of having successful sexual intercourse with injection therapy - Good efficacy even at the 4 year timepoint.
Mulhall 1999[124]	Retrospective survey	- Survey mailed to 1,424 patients who had been prescribed ICI therapy. 720 men	- 31% of men dropped out at a mean follow up of 38 months. - Main reasons for dropout were cost of

		responded.	therapy, patient and partner problems with the concept of penile injection, lack of partner availability or spontaneous improvement in erections.
Shabsigh 2000[125]	Prospective cohort study	- Men who had failed sildenafil and were then started on ICI	- 67 men - Increases in the ability to attain an erection sufficient for erection and maintain an erection - 85% of men had improvements in IIEF
Hsiao 2011[126]	Retrospective survey	- 122 patients who were enrolled in a structured home injection program.	- At follow up 65% of men in the study were still using ICI. -Using the satisfaction domains of the IIEF, men reported significant increases in both erectile function as well as satisfaction as scored by the IIEF.
Nelson 2013[127]	Prospective cohort study	- 124 men in a structured penile rehabilitation program post radical pelvic surgery for cancer - Given surveys of pain and anxiety at baseline and 4	- Injection pain was rated to be low throughout - There was high anxiety levels associated with injections at the first dose. - The level of anxiety decreased at the 4 month mark - Over 40% of men

		months.	continued to report high anxiety associated with injections

Table 5: Studies Comparing Intracavernosal Injection to Other Treatments

First Author	Treatment	Design	Study Arms	Efficacy and Other Outcomes
Shabsigh 2000[153]	MUSE vs ICI	Crossover, randomized open label multicenter study	- Study of 111 men with erectile dysfunction of at least 6 months duration.	- More EDEX than MUSE administrations resulted in an erection sufficient for sexual intercourse (82.5% versus 53.0%) - Significantly more patients using EDEX achieved at least one erection sufficient for sexual intercourse (92.6% versus 61.8%; P <0.0001) - EDEX use resulted in a significantly greater percentage of patients attaining at least

				75% of erections sufficient for sexual intercourse (75% versus 36.8%; P <0.0001).
Shokeir 1999[154]	MUSE vs ICI	Prospective randomized study	- 60 consecutive men were randomized - 20 ug of injection alprostadil - 1 mg of MUSE.	- After 3 months of home treatment, patients had administered a total of 242 doses of intracavernosal PGE1 and 360 doses of MUSE - Intercourse was reported after 206 (85%) and 198 (55%) administrations of PGE1 and MUSE, respectively (P<0.05). - The most common adverse reaction was urogenital pain, reported by 47% of patients in the ICI group and

				7% of patients in MUSE group (P<0.05). - Home treatment was assessed as easy by 40% of patients in the ICI group and 90% of the MUSE group (P<0.05).
Soderdahl 1997[155]	ICI vs VED	Prospective randomized crossover study	- 50 couples were enrolled. - Half underwent ICI therapy for 15 uses and then used the VED for 15 uses and filled out satisfaction questionnaires after 15 uses. - The other half of the group used VED first followed by ICI.	- Patients and their partners reported a superior quality of erections with the injection method but the difference did not reach statistical significance. - The ability to attain orgasm and the overall satisfaction of the patient and partner with the sexual experience was significantly better when using injections.

Presentations

Erectile Dysfunction Medical Treatment Presentation 1

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