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Nonsurgical Treatment of ED: A Review of Current Options

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Introduction

The integration of psychological, neurological, and vascular mechanisms that combine to trigger a physiologic response inside the vasculature of the penis is required to achieve penile erection. Erectile dysfunction (ED) is becoming more common among men, and it has an impact on both their own and their loved ones' quality of life. Diabetes mellitus, hypertension, hyperlipidemia, smoking, and vascular occlusive disease are all causes of vasculogenic ED.[1] The majority of men's ED treatments are currently centered on medication. Since the historical introduction of papaverine in the early 1980s, pharmacotherapy has progressed. The first medicine licensed for ED was alprostadil injections (IC injections). Sildenafil was a breakthrough as the first orally administered drug approved for ED. PDE5 inhibitors are an orally administered medication that has been licensed for the treatment of ED and are the only pharmacological classes that have evolved as a result of technological advancements.

Men with ED who are not satisfied with PDE5i therapy have the treatment option of a vacuum erection device, intraurethral alprostadil and intracavernosal injections.

LI-ESWT (low-intensity extracorporeal shockwave therapy) is a 'hot topic' in the field of ED, both in the medical community and in the general public. The ideal patient population for LI-ESWT and defining important technical parameters (number of shocks, energy level, location of probe application, number/timing of sessions) have yet to be fully defined.[2] In this article we reviewed various literatures on pharmacotherapy and LI-ESWT for treatment of ED and compiled the outcome to enable the practitioners to choose right approach for their patients.

PDE5 Inhibitors

PDE5 inhibitors are not erectogenic drugs. They require the presence of sexual arousal and NO production. They potentiate the NO effect and they can be considered facilitators for penile erection. Their effect also requires the presence of adequate and efficient smooth muscle cells in the CCs.[3,4] Table 1 lists the Food and Drug Administration's and the European Medicines Agency's directions for use (labeling) for the four widely available PDE5 inhibitors.

Table I: *Information for the Use of the Four Widely Available Phosphodiesterase Type 5 Inhibitors (On-demand Use)*

	Avanaûl	Sildenaûl	Tadalaûl	Vardenaûl
Food and Drug Administration	As soon as ~15 min before sexual activity	~1h before sexual activity	No speciûc timeframe provided	~60 min before sexual activity
European Medicines Agency	~15-30 min before sexual activity	~1h before sexual activity	~ 30 min before sexual activity	~25-60 min before sexual activity

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The effectiveness and safety profiles of all PDE5 inhibitors are excellent. There is no indication that one PDE5 inhibitor is more effective or has fewer side effects than another.[5] Patients who have been treated with various PDE5 inhibitors have reported similar levels of improvement. Patients should be offered the option to try a variety of PDE5 inhibitors in every scenario. This method promotes patient satisfaction and compliance.[6] Moreover, dose titration for a given PDE5 inhibitor to the maximum tolerated dose is strongly recommended because it increases efficacy and satisfaction from treatment.[7] Despite the positive clinical results, there are considerable dropout rates. Cost, insufficient efficacy, and adverse events (although the latter is rarely a reason of dropout) account for up to 50% of patients discontinuing treatment.[8-9] PDE5 inhibitors can also be utilized in conjunction with IC injections. In patients who did not respond to IC injections (high-dose alprostadil or tri-mix), a combination of sildenafil (100 mg) and tri-mix injections was shown to be effective in 31% of cases.[10] However, the data are very limited and a recommendation cannot be given.

IC Injection Therapy

Several medication combinations have been introduced in addition to alprostadil, which is still the sole medicine approved for IC injections worldwide. In more than 70% of men with ED of psychogenic, organic, or mixed etiology, IC alprostadil produces an ideal erectile response favorable to sexual satisfaction, as well as a considerable increase in stiffness ratings. Overall, it is very well tolerated with only a few side effects. A mild form of local pain has been reported in 11% after self-injection but it decreases over time and can be minimized by coadministration of sodium bicarbonate or procaine. Penile ecchymosis has been reported in 8%, whereas priapism and cavernosal fibrosis are very rare (1% - 2%), when PGE1 is used as monotherapy.[11-13]

IC Papaverine is also an option which is less used. In 615 patients followed for 8 years, normal erectile capacity returned in 91% receiving IC therapy with papaverine hydrochloride alone or with an a-blocker (bi-mix).[14] The drug is considered cost-effective. However, specific side effects preclude its use as a monotherapy. Within the pharmacologic dose range (10e60 mg), the notable untoward responses include prolonged erection and/or priapism, with fibrotic changes and penile curvature with long-term usage.[15] A bi-mix is an admixed combination of papaverine and the competitive a-adrenoceptor blocker phentolamine that is approved for clinical usage in some European countries.

In the therapeutic environment, the technique of self-administration of IC injectable therapy should be explicitly demonstrated to prospective users.

The use of an ultrathin needle (27-30 g) to inject the medicine into the CC through the lateral aspect (3 or 9 o'clock) while avoiding unintended harm to the mid-dorsal structures should be stressed in the instructions. Self-injection of vasoactive agents is difficult, if not impossible, in those with poor visual acuity or manual dexterity and morbid obesity. pharmacologically induced prolonged erection and priapism are more common with the combination of vasoactive agents. Penile fibrosis is another drug-dependent complication after long term IC administration of vasoactive agents. Comparative evidence has pointed to average incidences of 1% for PGE1 and 6% to 12% for papaverine and its premixed combinations.[13] Dropout issues are important. Several causes have been identified, including cost constraints, discomfort or pain, subjective lack of satisfaction or spontaneity with the erectile response, and needle phobia or other psychological issues.[13-15]

Intraurethral alprostadil

In 1994, PGE1 (alprostadil) was used in an alternative medication delivery method. A tiny applicator is pushed into the meatus to deposit a single dose of alprostadil into the moistened urethral mucosa. The drug transfuses into the cavernosal bodies to elicit the pharmacotherapeutic effect. Intraurethral application require approximately 50 times the IC dose of PGE1 for the same therapeutic efficiency. The effective dose of PGE1 significantly

increased the main outcome measurement (successful intercourse at home) compared with placebo (64.9% vs 18.6% in 1,511 men and 69% vs 11% in 249 men with organic ED).[16-17] Local pain or burning sensation not amounting to personal distress has been commonly reported by 25% to 43%, with minor urethral bleeding in 1% to 5% of users. There have been no citations of urethral stricture, priapism, or cavernous fibrosis secondary to transurethral PGE1. It might be of benefit in non-responders to PDE5 inhibitors as a combination therapy (intraurethral alprostadil plus PDE5 inhibitor). A specific indication for intraurethral alprostadil monotherapy is the rare condition of cold or soft glans syndrome.

Vacuum Constriction Devices

VCDs (vacuum constriction devices) are a well-known ED treatment method [18]. They engorge the corpora cavernosa passively, using a constrictor ring around the root of the penis to keep blood in the corpora. As a result, these gadgets' erections aren't natural because they don't use physiological erection pathways. Efficacy in terms of erections suitable for intercourse can be as high as 90%, regardless of the ED's etiology.[18,19] Satisfaction rates range between 27% and 94%.[20,21] Men with a motivated, interested and understanding partner report the highest satisfaction rates. Data on different subpopulations such as patients with spinal cord injuries, those who have undergone radical prostatectomy, patients with diabetes, those with ED due to psychogenic causes and even those patients who have undergone explantation of penile prostheses, support high efficacy and satisfaction rates.[22] Contraindication of VCD is coagulopathy.

Low-intensity extracorporeal shockwave therapy

LI-ESWT treatment is used for tissue repair and regeneration. It is believed that acoustic shock waves carry energy, and when targeted and focused, interact with the targeted deep tissues causing mechanical stress and micro trauma; hence, its effect on erectile tissue can be explained. Vardi *et al*.[23] showed that LI-ESWT has a positive short term clinical and physiological effect on erectile function. A different clinical trial was undertaken by Kalyvianakis et al.[24] which looked at the effect and safety of varying the number of sessions, frequency, and repetition on erectile function. Patients were separated into two groups: Group A received LI-ESWT therapy once a week, and Group B received LI-ESWT therapy twice a week for six weeks. The patients were monitored for a period of six months. With an increase in total session numbers, frequency of sessions/week, and recurrence of therapy within 6 months, Kalyvianakis et al.[24] found an increased effect on erection and sexual performance, with no further side-effects. Srini et al.[25] revealed substantial increases in the IIEF-EF and EHS domains during a 12-month follow-up after LIESWT. However, because of the significant dropout rate, these findings are seriously skewed. In the majority of RCTs, erectile function improved only somewhat. Patients with ED as a result of severe pelvic procedures appear to have a slim probability of regaining erectile function and receive little benefit using LI-ESWT.

Conclusion

Because of their high efficacy and safety profile, PDE5 inhibitors remain a first-line therapeutic choice. New compounds and formulations are constantly being explored for this class of medications. Intracavernosal injections remain a well-established therapy option, while intraurethral and topical alprostadil offer a less invasive alternative. The literature's contradictory results on the effect of LI-ESWT could be due to a number of factors. Because the current evidence is encouraging but still disputed, no clear clinical recommendation for LI-ESWT for ED can be made, and more high-quality research are required.

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