A historical review of erectile dysfunction

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Over the last three decades, there has been a significant increase in our understanding of the physiologic mechanisms responsible for erectile dysfunction. Erectile dysfunction has become a topic of considerable media and societal interest and acceptance. Paralleling the increase in knowledge has been an explosion in therapeutic options. This article will evaluate the therapeutic options, from a historical perspective of what has been available, and outline the progress that has been made.

Key Words: erectile dysfunction, therapeutic options

Introduction

Medical understanding of erectile function and erectile dysfunction (ED) in the human male has improved considerably in recent years. Incidence, prevalence, and etiology of, as well as risk factors for, ED have been better defined – the physiology and pathophysiology of erection and ED are now better understood. This in turn has led to improved treatments particularly in the area of noninvasive, medical therapies. The treatments that have been available over the last 30 years will be examined in this article, to show the remarkable progression from invasive, seldom-used procedures, to convenient, safe, and effective oral agents. Although sexual therapy or counseling is an essential component of treatment, and is an option used alone or in combination with other therapy, it will not be discussed in this article.

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Treatment

Historically, local pharmacological treatments for ED started in Arabic, Greek, and Roman times, when a myriad of herbal ointments and medications were applied locally to the genitals to enhance "vigor" and "strength."[1] The modern era of medical treatment for ED began with surgical innovations in the 1970s, and has since progressed to less invasive and more convenient therapeutic options. These will be reviewed, roughly in chronological order based on their time of introduction into clinical practice.

Surgical treatment

Surgical treatment for ED was introduced in the early 1970s, as the first effective medical treatment for what was then called impotence.[2]

There are two broad categories of penile prostheses: semi-rigid and inflatable. The semi-rigid prosthesis consists of paired silicon rods of varying length and girth with a twisted metal wire of silver or stainless steel in the centre. Several manufacturers market similar prostheses and the choice of the model is left to the discretion of the surgeon and patient, recognizing that cost and a particular surgeon's experience with different models influence this decision. Malleable prostheses are relatively easy to surgically implant, easier for the patient to use, have less chance of mechanical failure, and cost less. However, the unnatural constant erection, less concealability, and inability to adjust girth have made this form of prosthesis unfavorable to many patients. The use of semi-rigid prostheses has been declining in favor of inflatable prostheses.

The inflatable prosthesis is a three-piece device with paired cylinders, a scrotal pump, and a pelvic reservoir Figure 1. The system is generally filled with normal saline. The reservoir is commonly placed in the retropubic space and is readily concealable. It provides the best flaccid status while deflated, as well as optimal concealment. The inflatable prosthesis produces the most natural appearing erection. Although in the initial phases of production complications occurred due to leaks and infection, with refinement and modifications of these prostheses, the complication rate is no more than with the semi-rigid prosthesis.[3] Other types of inflatable prostheses less commonly used include a two-piece device (reservoir combined with pump, implanted in the scrotum) and a one-piece device (with reservoir and pump included within each cylinder).

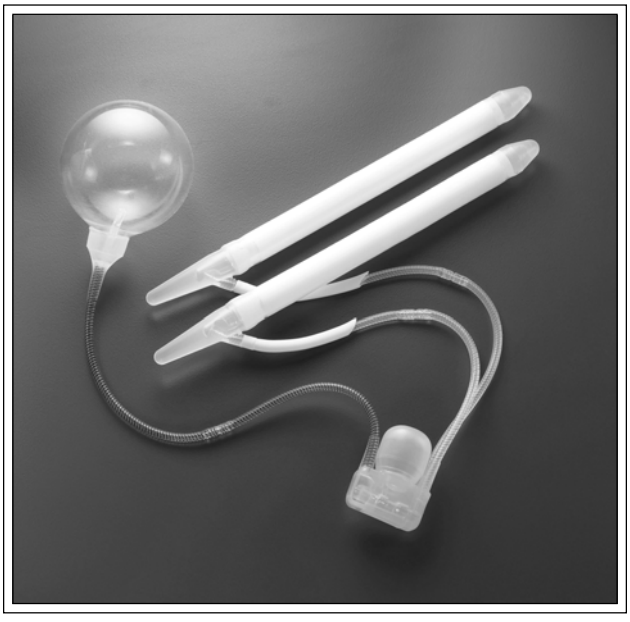

Figure 1. Three-piece inflatable prosthesis. Photo supplied by American Medical Systems Inc., Minnetonaka, MN.

Patients with severe ED who do not respond to any nonsurgical therapy can be considered candidates for a penile prosthesis. Although the percentage of such patients will be small compared to the total number of patients with ED, prosthesis implantation remains an option for this specific patient population. Suppliers claim that sales of penile prostheses have been relatively stable in the last decade.

Topical therapy

Drugs that possess vasodilatory effects have been used topically for the treatment of ED, although with little clinical or commercial success. Nitroglycerin, a potent vasodilator of coronary arteries, has been used topically in the form of ointments, pastes, or patches for the treatment of ED. Two percent nitroglycerin paste applied to the penile shaft has been demonstrated to increase the diameter of penile blood vessels. However, the clinical response rate in achieving a "usable" erection has been low.[4] Severe headache associated with nitroglycerin administration has prohibited its routine use as a therapeutic modality. Minoxidil as a topical agent (Rogaine®) is known to induce vasodilation in the microcirculation around the hair follicles, increasing cutaneous blood flow. A few anecdotal reports have indicated that penile rigidity increases with minoxidil, but no significant changes occur in erectile response to visual stimulation or in penetration capability.[5] Topical prostaglandin E (PGE) and topical papaverine in a gel form, unlike intracavernous injection, have not been shown to produce a significant response in patients with ED.[6]

Injection therapy

The early 1980s saw the introduction of injection therapy, which was based on the recently gained knowledge of the role of vasoactive substances in penile erection.[7] Initially, papaverine was the pharmacologic agent used, although priapism and intracavernous fibrosis were complications. In 1986, prostaglandin E1 (PGE1) was commercially introduced as a self-injection treatment alternative for ED, and it remains a commonly used preparation (at a dose of 10 μg or 20 μg). Several combinations of vasoactive drugs were subsequently investigated. A currently used combination, triple mix therapy (referred to as Trimix), contains PGE1 5.8 μg, papaverine 17.6 mg, and phentolamine 0.65 mg in 1 mL of water or saline. It is usually formulated in hospital pharmacies and

dispensed with a prescription. An injection trial in the office or hospital in conjunction with a teaching session of intracavernous injection procedures precedes a program of self-injection at home. The volume of injection is titrated according to response, with an initial dose of 1 mL. The rate of priapism (prolonged erection beyond 4 hours) associated with intracavernous injection of Trimix is low, and if priapism occurs it can usually be overcome with a cold shower, physical exercise, and intracavernous injection of adrenergic agents.

When it was introduced, intrapenile injection therapy was quite widely used in the treatment of ED. It is now generally limited to those patients not responding to oral agents, or to those men who may have contraindications such as the use of nitrates.

Moxisylyte is a competitive α-receptor antagonist that has been used as an intracavernous injection in a range of between 10 mg and 30 mg doses. Moxisylyte can induce an erection that is adequate for intercourse in most ED patients.[8] To date, however, it has only been approved for the treatment of ED in Europe, likely due to an inadequate number of randomized controlled trials establishing efficacy and safety to meet Health Protection Branch requirements. Moxisylyte appears to be less effective than papaverine, but with fewer adverse effects such as penile pain and priapism. It has been suggested by Buvat and colleagues as a potential first-line injection treatment for ED, to be assessed before resorting to alprostadil or papaverine.[8]

Vacuum constricting devices

With vacuum constricting devices (VCD) using negative pressure to distend and fill the corporeal sinusoids, and an external constriction ring to prevent venous return, a satisfactory erection can be produced and maintained. These devices have been available since the late 1980s. Current VCDs are commercially available without a prescription and consist of a suction cylinder and pump to induce erection, as well as a constricting band placed at the base of the penis to maintain the erection Figure 2. The device should not be used for longer than 30 minutes at a time in order to prevent ischemia of the penis. Complications of VCD are usually minor and include petechiae, ecchymosis, and dusky discoloration of the glans.[9] A clinical trial in 216 consecutive patients using the device reported 82% to 89% patient and partner satisfaction. However, only 42% of patients were long-term users, with the remainder discontinuing after a period of up to 16 weeks. Other reports confirm these results. One study by Dutta and colleagues in a group of 129 men reported an overall discontinuation rate of 65%.[10]

Figure 2. Vacuum therapy for ED. Photo supplied by Soma Blue Medical Systems, Inc., Augusta, GA.

The VCD, a nonpharmacological method to achieve and maintain erection, has found a specific place in the management of men with ED. It continues to be a popular, cost-effective approach for men who are unwilling or unable to use pharmacological therapy, and who decline to undergo penile prosthetic surgery.

Transurethral therapy

Prostaglandin E1 has also been used transurethrally in the form of MUSE®, Medicated Urethral System for Erection. The alprostadil is in the form of a pellet that is delivered through an applicator inserted into the urethra Figure 3. More than 50% of men receiving a

Figure 3. Medicated urethral system for erection (MUSE®). Photo supplied by Paladin Labs Inc., Montreal, QC.

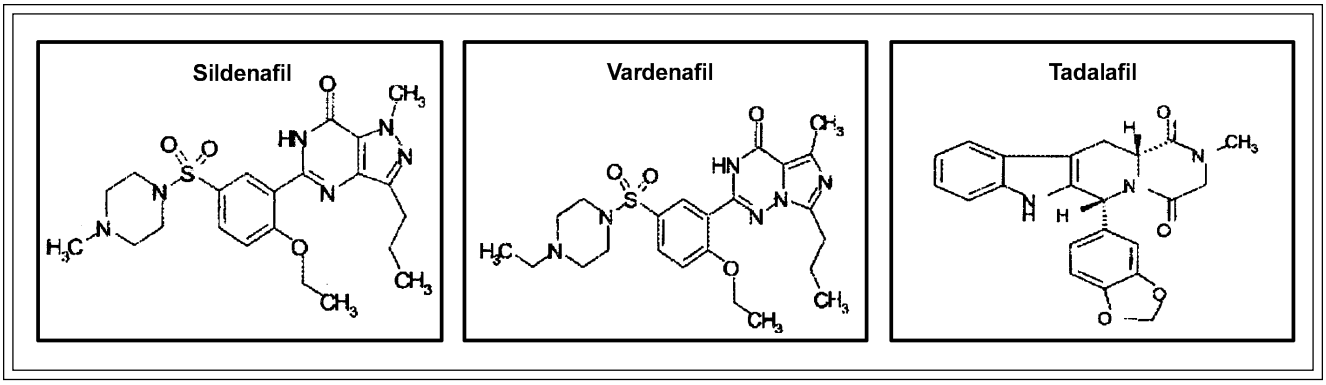

Figure 4. Molecular structures of sildenafil, vardenafil, and tadalafil.[13]

500 μg dose of alprostadil (synthetic prostaglandin) transurethrally are reported to have achieved rigid erection.[11] This regimen necessitates that the patient and physician work together to titrate the dose of alprostadil from 250 μg to the 1000 μg dose as required. The procedure, however, was discontinued in a small percentage of patients due to urethral pain.

This less invasive therapy to self-injection was the victim of poor timing on entry to the market as the first oral agent, sildenafil, was introduced soon after its commercialization.

Oral pharmacotherapy

The advent of the first oral agent for erectile dysfunction, sildenafil, has had a major impact on the management of ED. Sildenafil is an orally active, potent, and selective inhibitor of cGMP-specific phosphodiesterase type 5 (PDE5).[12] Sildenafil enhances the relaxant effect of nitric oxide (NO) released in response to sexual stimulation by increasing cGMP concentration in the corporeal smooth muscle. It is absorbed rapidly after oral administration, with peak plasma concentration in the fasting state between 30 to 120 minutes. Dietary intake produces an interaction, with a high fat meal delaying the peak plasma concentration of sildenafil, which may influence its efficacy and convenience among users. The convenience of oral PDE5 therapy for ED means that these drugs have virtually supplanted all other agents, or at least relegated them to niche status. Concerns with cardiac safety in men taking nitrates for heart disease concurrently with sildenafil have been the significant negative finding with this agent – this is discussed in more detail in the fifth article in this series.

The success of sildenafil as an oral therapy for ED has stimulated a high degree of interest in new drug development. Two new PDE5 inhibitors will soon be released in Canada. Figure 4 shows the molecular structures of these three agents.[13] As can be seen, sildenafil and vardenafil have a very similar structure whereas tadalafil is different. The pharmacology of PDE5 inhibitors, and the clinical findings with tadalafil, will be reviewed in other articles in this supplement.

Apomorphine-SL (Uprima™) is a dopamine receptor agonist that acts directly in the central nervous system.[14]

Apomorphine has demonstrated a rapid onset of action due to its rapid absorption. In the subset of one study, apomorphine at a sublingual dose of 3 mg was compared to placebo.[15] In the apomorphine group, all key outcomes were significantly higher: attempts of intercourse, overall assessment of erectile function, and overall assessment of satisfaction with intercourse. Men taking apomorphine did have a higher rate of nausea versus placebo (7.0% compared to 1.1%).[15]

Conclusion

Oral drug therapy is now well established for the treatment of ED. Guidelines for the management of ED published by the Canadian Urological Association in 2002 recommend oral agents as the first-line therapy.[16] Currently available oral agents are simple to use, effective, and have few serious side effects. Other forms of therapy have been relegated to second-line and third-line options after oral therapy has failed or is not tolerated by a patient. The future will undoubtedly see further developments of additional oral treatments for ED. As a result, with few exceptions, other forms of treatment may well become redundant and be replaced almost entirely by oral pharmacotherapy for ED. □

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