Review Article

The devil is in the details: an analysis of the subtleties between phosphodiesterase inhibitors for erectile dysfunction

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Abstract: Erectile dysfunction (ED) is a common sexual disorder with numerous etiologies involving multiple organ systems that leads to significant distress and decreased quality of life for the affected men. Fortunately, there are several modalities and interventions for treating ED. Oral medications, intra-urethral compounds, intracorporeal injections, vacuum-assist devices and surgically implanted prostheses are all part of the treatment algorithm. One of the first-lines and certainly the most widely used options for treating ED is the family of oral phosphodiesterase type 5 inhibitors (PDE5I). The introduction of these medications in the late 1990s revolutionized the field of sexual medicine. Currently there are no guidelines and minimal literature to help providers choose among drugs in this class. This review will address differences in efficacy and side effects between various members of the oral selective phosphodiesterase-5 inhibitor class of drugs.

Keywords: Erectile dysfunction (ED); phosphodiesterase 5 inhibitors (PDE5I); efficacy; side effects

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Introduction

Erectile dysfunction (ED), as described by the National Consensus Conference on Impotence, refers to the inability for a male to participate in sexual activity due to inadequate erection (1). Survey results from the Massachusetts Male Aging Study showed an overall prevalence of ED of any type in 52% of men surveyed. Between the ages of 40 and 70, the prevalence of complete ED tripled to 15%. This survey also showed a correlation with several disease processes including hypertension, diabetes and several classes of medications. Not surprisingly, as age increases the incidence of ED increased (2). With upwards of fifty-percent of men over the age of 40 affected, there is a high degree of disease burden worldwide. With such a high incidence of disease burden, the demand for treatment is high. This was highlighted when sildenafil was released to the market in 1998, quickly becoming one of the most successful drugs in history. In the 7 years following its release, sildenafil was prescribed to more than 23 million men world-wide by 750,000 providers (3). By the year 2005, Medicaid was spending $15 million per year on PDE5I's. In 2005, the Congressional Budget Office projected that it would be spending around $2 billion on pharmaceutical treatment of ED over a 10-year period (4).

From a biologic standpoint, the process of attaining an erection is a complex process involving the adequate function of multiple organ systems: the neuronal axis, vascular anatomy and the hormonal axis. At its core, penile erection and detumescence are hemodynamic events controlled by neuronal input, with the cavernosal smooth musculature playing a vital role. Sexual activity and increase in parasympathetic activity lead to vasodilation and increased blood flow, causing an increase in intracavernosal pressure (5). Key to this process is the cascade involving nitric oxide and cyclic guanosine monophosphate (cGMP).

Activation of this chain leads to relaxation of the corporal smooth muscle and eventual erection (6).

Since nitric oxide and cGMP play an important role in erectile function, focusing research on their manipulation led to the identification of phosphodiesterases as key players in the chemical cascade responsible for erectile function. PDE5 (phosphodiesterase type 5), a phosphodiesterase subtype specific to cGMP, was found to have abundant expression in the corpus cavernosum, and expression of PDE5 led to degradation of cGMP and thus penile detumescence. Inhibition of PDE5 led to increased levels of cGMP and cavernosal smooth muscle relaxation (7,8). This breakthrough led to the development of the first PDE5Is for the treatment of ED in men.

In 1998, the first oral pharmaceutical that targeted this cascade was released. Sildenafil, a selective inhibitor of phosphodiesterase 5, was approved by the FDA and became a breakthrough in the management of ED. Since the early 2000s, tadalafil, vardenafil and avanafil have all joined sildenafil as FDA-approved oral therapies for ED. Each particular pharmaceutical has a slightly different biochemical profile with consequent differences in efficacy and side effects in patients using these oral therapies. This review paper will address these differences and compare the varying efficacies and side effects of the various PDE5Is.

Discussion

Below we review the most common phosphodiesterase-5 inhibitors individually with comparison between their efficacies and side effects.

Sildenafil

Sildenafil was the original PDE5I and the first to enter the market in 1998. Pharmacologic studies show that the compound is a selective inhibitor of PDE5, though there is some cross-reactivity with other phosphodiesterase subtypes. This cross-reactivity creates some of its side-effect profile (9). Initial studies showed a dose-dependent response among users with significant improvement in erection quality. Overall, 69% of men were able to achieve an erection suitable for intercourse versus 22% for those receiving placebo. Safety and efficacy was assessed with doses of 25, 50, and 100 mg. Sildenafil was found to have favorable pharmacokinetic profile with rapid absorption and onset. Efficacy was reported in as little as 30 minutes and it has a plasma half-life of 3–5 hours (10). The most frequently reported side effects were rhinitis, dyspepsia, headache, flushing and headache. These were found to occur in anywhere from 11–18% of patients (11,12). Visual changes including altered color perception and 'star vision' were also reported (1%). Visual changes have become a hallmark for sildenafil, with its increased cross-reactivity with phosphodiesterase type 6. These side effects were short-lived and there were no reports of serious side effects attributed to sildenafil (12). Studies since sildenafil's release have also shown that re-education on the drug, medical optimization, scheduled dosing and dose escalation can further increase response rates. Fifty-four percent of original non-responders had significant improvement in the quality of their erections with these interventions. The majority of these men required doses of 100 mg (13). Overall, sildenafil has proven to be a ground-breaking option in the treatment of ED. Its wide success has led to the development of multiple PDE5I's for the treatment of ED.

Vardenafil

Vardenafil is a fast-acting PDE5I that first came to market in 2003. Vardenafil is prescribed in both 10mg and 20mg formulations. Intake of this compound leads to rapid increases in plasma concentrations, with an average plasma half-life of 4.2 hours. Again, impact was rapid with increases in erectile function as early as 24.2 minutes after taking the medication. (14) Like sildenafil, vardenafil was found to be an effective option for the oral treatment of ED. A randomized, double-blind, placebo controlled study showed promising results. The mean ability to achieve erection adequate for penetration increased from 40.9% to 80.5%. Rates of successful intercourse improved from 14.7% to 65.4% at the end of a 12-week trial (15). Vardenafil had a similar safety and side effect profile when compared to sildenafil. Headache, flushing, dyspepsia and rhinitis were again the most common side effects. Unlike sildenafil, there were no reports of abnormal visual distortions. There were no serious drug-related side effects (16). There were also thoughts that once-daily dosing may be advantageous; however, as compared to standard on-demand dosing, once-daily dosing did not result in better erectile function or satisfaction for those men with mild-to-moderate ED (17). In a randomized, double-blind, head-to-head trial with sildenafil, vardenafil was found to be non-inferior. Nominal significance was found in favor of vardenafil when looking at erectile function and quality (18).

Tadalafil

Tadalafil was the third PDE5I brought to the market for treatment of ED with its FDA approval in 2003. Like its counterparts, tadalafil was found to have a significant effect on erectile function across a wide range of ages and disease processes and severities (19). In an early study, 81% of men reported improved erection quality as compared to only 35% of those enrolled in the placebo arm. Tadalafil is also well-tolerated (20) though mild side effects have been reported. These include headaches, dyspepsia and backache. Myalgias were reported in 3% of men (19). This is now known to be due to a cross-reactivity with PDE11. Importantly, the pharmacokinetics of tadalafil are quite different than the PDE5Is approved prior to its arrival on market. Tadalafil has the longest duration of action at 24–36 hours. Onset of action is similar at 30 minutes (21). This prolonged period of efficacy has been seen as advantageous for some men. Tadalafil is also unique in that it is the only PDE5I that is approved for once-daily dosing, useful for men with both ED and lower urinary tract symptoms attributable to BPH (22,23). While this may come into consideration when choosing between PDE5-I's, we will not address its use for lower urinary tract symptoms. Once-daily doses are lower at 2.5–5 mg with medication accumulation due to the prolonged half-life. General satisfaction with once-daily dosing for ED is believed to be high with 86% of men on once-daily dosing continuing after six months (24). It must also be noted that unlike other PDE5Is, tadalafil is not affected by ingestion of fatty meals.

Avanafil

Avanafil is the latest oral PDE5I to receive approval by the FDA for treatment of ED in 2012. Like the other PDE5Is, avanafil is a potent competitive inhibitor of PDE5. It shows a higher selectivity for PDE5 versus PDE6 compared to sildenafil and vardenafil. Time to peak response was found to be 10 minutes for avanafil, versus 30 minutes for sildenafil (8,25,26). Avanafil was also found to be have moderate durability of effect with response at more than 6 hours from ingestion (27). Flushing and headache were again the most common side effects, but usually transient and only mild to moderate (28). Furthermore, the actual rates of the most common side effects were particularly low (ranging from 1.6–3.7%) (26). Fewer than 2% of patients discontinued therapy due to an adverse drug reaction in one study (29). Interestingly, avanafil had lower rates of hypotensive episodes (15%, 29% and 12% for avanafil, sildenafil and placebo) with monitored co-administration of nitroglycerine in males (30). This might suggest a possible role for use in patients with concurrent nitrate use, though this particular study was performed in healthy volunteers without cardiac histories. With its fast onset and limited side-effect profile when compared to other PDE5Is, avanafil may be well-suited for the majority of patients.

Comparison of phosphodiesterase-5 inhibitors

As study after study has shown, PDE5Is are well-suited for use in the treatment of ED. As a group, they are generally well-tolerated and lead to a significant increase in erectile functions, sexual satisfaction and quality of life. With such favorable attributes, the American Urological Association made this class of drugs first-line treatment for ED in those men in whom it is not contraindicated (31). The European Urological Association has also released guidelines placing PDE5Is at the forefront of treatment of ED (32). These guidelines make no specific differentiations amongst PDE5Is or discuss particular treatment algorithms. Differences between specific drugs are acknowledged, but drug selection is left up to provider and patient preference. This lack of direction on PDE5I drug choice is attributed to a lack of data and comparative research at the time of release of the guidelines. Since that time, there have been multiple attempts at such comparisons.

No one study has directly evaluated the efficacy of all FDA-approved PDE5Is against each other. Rubio-Aurioles *et al*. compared outcomes between tadalafil (both PRN and once-daily) and sildenafil in a randomized, open-label trial. Not surprisingly, they found that both tadalafil regimens led to higher ratings with sexual self-confidence, timing concerns and spontaneity. There was no significant difference in quality of erection (18). These results were similar to those found in an open-label, randomized, cross-over trial by Bai *et al*. Again, both drugs improved erectile function and quality. In this particular study, 69.1% of men preferred tadalafil due to its longer efficacy (33). Since the incident of side effects is generally low for both drugs, neither of these studies were able to find a significant difference in side effects.

With timing obviously being important to users, knowledge of pharmacokinetics of the various formulations of the PDE5Is is important. Although the timing of onset is similar amongst these drugs (34), tadalafil has the longer half-life (34). In terms of rapid onset of effect, avanafil may

Table 1 T (1/2) and time of onset for four common phosphodiesterase-5 inhibitors

Drug	Dosage	Timing relative to intercourse	Onset (min)	Duration (h)	Mode of metabolism
Sildenafil	50–100 mg	1 h	14–60	≈4	Hepatic
Tadalafil	10–20 mg/5 mg daily	1–12 h	16–45	≈36	Hepatic
Vardenafil	10–20 mg	1 h	25	≈4	Hepatic
Avanafil	50–200 mg	30 min	30–45	≈6	Hepatic

hold a small advantage (21). In *Table 1* below, one can find a review of the relevant pharmacokinetic factors for each drug.

With the goal of comparing the current PDE5Is available at the time (sildenafil, vardenafil and tadalafil), Tsertsvadze *et al*. employed meta-analysis to help direct PDE5I use. Data from 130 randomized control trials were analyzed. Most of these trials were short-term studies looking at treatment efficacy with placebo control. All PDE5Is improved erectile function on validated surveys. Four trials comparing PDE5Is either showed no statistical improvement in successful intercourse, or minimal improvement. Importantly, differences in adverse events were not statistically significant between drugs. Tadalafil may have been associated with higher rates of myalgias. Discontinuation rates due to adverse events were low with all PDE5Is (35).

Another study attempted to look specifically at patient preference when trying to determine choice of PDE5I. This was a prospective, randomized, open-label, fixed-dose, preference study with cross-over design that attempted to compare efficacy and patient preference between sildenafil, vardenafil and tadalafil. Sildenafil 100 mg, vardenafil 20 mg, and tadalafil 20 mg were compared. Each drug was taken at least 6 times by each participant, at least 7 days of washout prior to switching medications. All three drugs showed significant improvement in erectile function as determined by their International Index of Erectile Function (IIEF) score. Tadalafil had statistically significant higher IIEF scores when compared to both sildenafil and vardenafil. Patient responses to direct questioning of preference mirrored these results (tadalafil had the highest preference rates at 52.2%). Rates for sildenafil and vardenafil were 27.7% and 20%, respectively. For those who preferred tadalafil, subjectively better erections and the possibility of intercourse the following day were the deciding factors (36). In an age where patient preference is a key component of care, these findings may prove key when recommending a PDE5I to your patient.

In an attempt to synthesize the large volume of data on PDE5Is, their efficacy and side effects, Chen *et al*. attempted to use a trade-off, network meta-analysis to better direct PDE5I use. This particular study compiled 82 trials with a total of 47,626 patients for efficacy analysis. Seventy-two trials and 20,325 were included for analysis of adverse events. Importantly, this analysis included PDE5Is that have yet to be approved by the FDA, namely udenafil and mirodenafil. In terms of efficacy, all drugs in this class were found to be efficacious when compared to placebo. Sildenafil 50mg was found to be the most effective, but also had the highest rates of adverse events. Vardenafil 10 mg (0.35 CI, 0.32–0.38) and avanafil 100 mg (0.29 CI, 0.15–0.44) had similar adverse event rates when compared to sildenafil 50 mg (0.47 CI, 0.34–0.59), but unfortunately their rates of efficacy were substantially lower (37). Overall, the authors suggested that for high efficacy, on-demand sildenafil 50 mg is the treatment of choice. For those patients where side effects are of strong concern, tadalafil 10 mg would be a reasonable choice while still maintaining efficacy.

Conclusions

The development and use of PDE5Is for the treatment of ED has revolutionized the quality of life for millions of men across the world. This class of drugs has become the first-line therapy for ED and will continue to play an important role for years to come. Importantly, studies have consistently shown that all approved selective PDE5Is are efficacious and lead to improved erectile function and sexual encounters. From that point, differences in drugs and choice of intervention should be based on patient preference, side effect profile, presence of concurrent lower urinary tract symptoms, and the desired half-life. Fortunately, the side effects for PDE5Is are uncommon, transient and low risk. Choice of a specific PDE5I should be directed by an in-depth conversation between provider and patient. Going forward, studies that compare the efficacy and side effects

among all approved PDE5I would shed significant light on developing a treatment algorithm.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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