Preference for and adherence to oral phosphodiesterase-5 inhibitors in the treatment of erectile dysfunction

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Abstract: Sildenafil was the first orally administered phosphodiesterase-5 inhibitor approved for the treatment of erectile dysfunction. Its successful introduction into clinical practice was soon followed by the launch of two other phosphodiesterase-5 inhibitors: vardenafil and tadalafil. The plethora of choices made the question "which PDE-5 inhibitor?" relevant for patients and clinicians. Despite the lack of head-to-head comparative trials it is widely accepted that there are no significant differences in their safety and efficacy. Therefore a number of studies set out to determine which of the inhibitors patients would prefer and reasons for that preference. The majority of published trials show a preference for tadalafil. Others have argued that preference trials have several methodological flaws and data favoring tadalafil with its long duration of action do not reflect real-life prescription filling and sales figures. But even if one of the available PDE-5 inhibitors is chosen to treat erectile dysfunction what is the long-term compliance? A significant percentage of men initiating treatment switch between inhibitors or discontinue therapy. Reasons for that seem to often be unrelated to efficacy or tolerability and include emotional and social factors determining couples' and individuals' sexual and treatment seeking behavior.

Keywords: PDE-5 inhibitors, sildenafil, vardenafil, tadalafil, preference, adherence

Introduction

Erectile dysfunction (ED) is a highly prevalent condition (Feldman et al 1994) affecting millions of men worldwide. Before oral phosphodiesterase-5 (PDE-5) inhibitors became available, intracavernosal injection of vasoactive drugs was one of the commonly prescribed medical treatments. Despite its proven efficacy, even in difficult to treat cases, many patients discontinued it for various reasons, including penile pain, unnaturalness of erection and fear of the needle, and loss of sex drive: in clinical trials, the patient drop-out rate has been as high as 47% (Hanash 1997). Similar to intracavernosal injection therapy, high drop-out rates have also been reported in clinical trials with intraurethral alprostadil, the other commonly prescribed ED treatment, and the most frequent reason for that was pain, either during the application or during erection and intercourse (Pangkahila 2000). Oral medication was expected to improve compliance compared with the above, relatively invasive, treatments.

In 1998, sildenafil became an US Food and Drug Administration-approved oral treatment for ED. In the years after that, two more PDE-5 inhibitors, vardenafil and tadalafil, were developed and also approved in 2003 for the same indication. Despite their common mechanism of action, the three PDE-5 inhibitors have molecular differences that are reflected in their pharmacokinetic properties and selectivity for different PDE isozymes (Carson and Lue 2005). With the exception of tadalafil's long duration of action, the impact of the molecular differences in clinical outcomes is negligible

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and all three drugs share good efficacy and satisfactory safety/tolerability profiles (Doggrell 2007).

There are currently more treatment options available for erectile dysfunction than ever. Oral pharmacotherapy is noninvasive, reversible, and easy to administer. Therefore PDE-5 inhibitors are the first option for treatment of ED for both patients and physicians (Hatzimouratidis and Hatzichristou 2005). It would be reasonable to assume that since oral PDE-5 inhibitors combine ease of administration, high efficacy, and good tolerability, compliance to long-term treatment would be high. Relevant reports, discussed in the adherence section of this review, indicate that despite initial enthusiasm a significant number of patients abandon treatment. The availability of three, more or less similar, drugs makes choosing one somewhat difficult and often patients switch from one to another. Given the lack of significant differences in efficacy and safety, treatment preference becomes increasingly important as adherence to the preferred drug would be higher.

Results from studies on PDE-5 inhibitor preference and factors influencing it as well on adherence to treatment published in peer-reviewed journals are reported in this paper and interpreted from a clinician's point of view.

Preference studies

A number of preference studies have been conducted so far aiming to determine patient preference for one PDE-5 inhibitor over another. Most of these studies have compared sildenafil and tadalafil, but a few have also included vardenafil.

In a multicenter, open label, fixed-dose, one-way crossover trial (Ströberg et al 2003), 147 patients using sildenafil 20, 50, or 100 mg as needed for at least 6 weeks prior to the study were assessed and then switched to tadalafil 20 mg as needed. Treatment-specific instructions were given with emphasis on the pharmacokinetic properties of the two PDE-5 inhibitors. 90.5% of patients preferred to receive tadalafil in a 6-month extension phase of this trial compared with 9.5% who preferred sildenafil. This preference seemed to be the same irrespective of patient age group, ED etiology and severity, and sildenafil dose at study entry.

At the same time another multicenter, randomized, double-blind, fixed-dose, two 4-week period crossover trial of tadalafil 20 mg or sildenafil 50 mg investigated men's preference for initiation of ED treatment (Govier et al 2003). Of 190 evaluable patients, 126 (66.3%) preferred to initiate treatment with tadalafil compared with 64 (33.7%) who preferred sildenafil. Patient age group, duration of ED, sequence of administration, previous exposure to sildenafil, and the presence of comorbidities (diabetes, cardiovascular disease) did not affect preference.

In 2004, a study assessing not only drug preference for tadalafil or sildenafil, but also dosing instruction preference was published (von Keitz et al 2004). In this randomized, double-blind, crossover trial, 219 patients were allocated to either sildenafil 50 mg or tadalafil 20 mg for drug preference assessment. Respective dosing instructions were given. Another 46 men were randomized to tadalafil 20 mg with either tadalafil or sildenafil instructions for assessment of dosing instruction preference while on tadalafil therapy. 66% of patients had used sildenafil prior to the trial and nonresponders to sildenafil were allowed in the study. A sham-placebo methodology was used to maintain the blind. Patients receiving sildenafil were offered the opportunity of an upward dose titration, but only 35% actually received it to mimic the pattern of sildenafil dose usage in the market. The remaining 65% received placebo dose titration, always in a double-blind fashion. In the drug preference assessment 73% of evaluable patients chose to receive tadalafil during an extension period compared with 27% who preferred sildenafil. In the dosing instruction preference assessment, 67% of patients preferred tadalafil dosing instructions.

In 2005, a multicenter, randomized, open-label, crossover trial of two 12-week treatment periods compared preference between tadalafil and sildenafil (Eardley et al 2005). 367 men with ED naïve to PDE-5 inhibitors received the recommended starting dose for both drugs initially and could titrate to their optimum dose before the assessment period. 48.4% of patients titrated to the 20 mg tadalafil dose while 30.6% titrated to 100 mg sildenafil. Of 291 men completing treatment with both drugs, 71% preferred tadalafil and 29% preferred sildenafil for the treatment of ED in an 8-week extension period. According to the authors, the small differences observed in certain efficacy parameters could not explain the difference in drug preference. In a later publication of data from this study (Dean et al 2006), tadalafil was significantly superior in improving patient psychosocial outcomes (Psychological and Interpersonal Relationship Scales [PAIRS] Domain scores) and this could probably account for the observed preference for tadalafil. In a post hoc analysis, baseline patient characteristics were not significantly associated with, and could not predict preference (Eardley et al 2007).

In 2006, a study evaluating in everyday clinical practice drug preference for the long-acting PDE-5 inhibitor, tadalafil, against the short-acting PDE-5 inhibitors sildenafil and vardenafil combined was published (Ströberg et al 2006). 186

ED outpatients eligible for treatment with PDE-5 inhibitors were prescribed eight tablets of the short-acting PDE-5 inhibitors at their maximum dose (4 tablets sildenafil 100 mg and 4 tablets vardenafil 20 mg) and eight 20 mg tablets of the long-acting inhibitor tadalafil. Respective instructions were given. Patients were advised to start with the short-acting tablets and use all doses before starting the long-acting ones without instructions for washout between drugs. Compliance to this regimen was not recorded. One third of the study population were naïve to treatment and the remainder already undergoing treatment with sildenafil (76 patients), vardenafil (6 patients), tadalafil (32 patients), or intraurethral/ intracavernosal medication (6 patients). 145 patients completed the programme trying all three drugs and 138 were considered responders. 55% of these patients preferred to continue their treatment with tadalafil, 27% with sildenafil, and 17% with vardenafil. Difference of preference between short- and long-acting was not significant (55% vs. 44%) in the entire study populationm, but naïve men seem to prefer the short-acting ones (60%) and nonnaive the long-acting inhibitors (64%).

Another multicentre, noninterventional, observational study assessing preference for sildenafil or tadalafil in clinical practice was also published in 2006 (Lee et al 2006). 2425 men changing treatment from sildenafil to tadalafil or vice versa participated in the study. Patients could choose between sildenafil and tadalafil, have no preference, prefer other treatment or prefer to stop treatment for ED. Of 1645 men taking sildenafil at baseline and changing to tadalafil, 70% preferred tadalafil, and 17% sildenafil. Of 679 men taking tadalafil at baseline and changing to sildenafil, 59% preferred tadalafil and 28% sildenafil. Data from this study published separately (Brock et al 2007) showed higher treatment satisfaction with tadalafil: authors stated that this might help explain greater preference for tadalafil. This was the first study to also assess physician ratings of patient preference as well as partner preference. Responses to the preference questionnaires showed that physician-rated patient preference, patient preference, and partner preference had a similar pattern all favoring tadalafil. Men who preferred tadalafil did so because of its longer duration of action and quality of achieved erections.

In the same year a prospective, randomized, open-label, fixed-dose, 3-period crossover study also included all three available PDE-5 inhibitors (Tolrà et al 2006). The same number of naive to treatment men, with moderate to mild ED, were randomized in one of 6 drug sequence groups for sildenafil 100 mg, vardenafil 20 mg, and tadalafil 20 mg, and had at least 6 tablets of each with 1 week washout period between them. Of 90 men who completed the protocol 27.77% chose sildenafil, 20% vardenafil, and 52.22% tadalafil in the drug preference assessment.

Preference for sildenafil or vardenafil has been assessed in men with ED and risk factors for cardiovascular disease (Rubio-Aurioles et al 2006). Data from two multicenter, randomized, double-blind, 2 – period crossover studies were pooled. 1057 patients with ED and a medical history/diagnosis of diabetes mellitus, hypertension, and/ or hyperlipidemia were randomized to receive sildenafil 100 mg or vardenafil 20 mg for 4 weeks. This was followed by a 1-week washout before switching to the other treatment. 931 men, 67% of whom had previously used sildenafil, were included in the Intent-To-Treat analysis. The overall preference was 38.9% for vardenafil and 34.5% for sildenafil. 26.6% of patients had no preference.

Adherence to PDE-5 inhibitor treatment

In an update on the safety of sildenafil published four years after its launch (Padma-Nathan et al 2002), 32% of patients in open-label extension of double-blind, placebo controlled clinical trials had discontinued study treatment by the end of the 3-year follow up. Nearly half of discontinuations occurred during the first year but most of them (79%) were not treatment related.

To investigate adherence to treatment in real-life, where patients initiate it outside the context of clinical trials, several studies have been conducted. Soon after the introduction of sildenafil into clinical practice the Dutch cohort of sildenafil users was formed to gather information on medication utilization patterns through pharmacy prescription recording (Souverein et al 2002). 317 men filling their first sildenafil prescription were followed up for a mean duration of 18 months: 153 had previously used ED prescription drugs and 164 had not. 48% of previous ED medication users and 45% of first time users discontinued sildenafil treatment during the follow-up period. Patients with a history of drug treatment for ED were nearly eight times as likely to switch to or re-start another ED prescription drug after discontinuing sildenafil compared to previously untreated users who tended to stop treatment for ED altogether. Age over 60 years, urinary incontinence, and use of insulin or antidepressants were associated with an increased likelihood of sildenafil discontinuation.

A retrospective evaluation of efficacy, safety, and drug utilization in 1187 outpatients initiating sildenafil treatment

between 1999 and 2001 was conducted through hospital database chart review, mailed questionnaires and telephone interviews (Jiann et al 2003). The prescription refill rate was 66% in responders and 26% in non-responders. In a more recent publication of data from the same institution (Jiann et al 2006), 57% of 444 successfully treated men (responded "yes" to the question "Did you have satisfactory sexual intercourse with Viagra® treatment?") had stopped using sildenafil at a mean follow-up of 3 years. The most common reason for that was effectiveness below expectations. Other reasons included high cost, loss of interest in sex, and inconvenience in obtaining the medication. Interestingly, adverse events were low on the list of reasons for discontinuation and the incidence of such events was higher in patients continuing treatment than in ones stopping it.

Discontinuation rate at 6 months and reasons for it were assessed by chart review or telephone interview in a cohort of 156 men whose erectile function was restored (International Index of Erectile Function [IIEF] score ≥26) with sildenafil treatment (Son et al 2004). 35% discontinued sildenafil medication. The reasons for it were primarily emotional or relationship-oriented and included shortcomings in the partners' or patients' emotional readiness for the restoration of sexual life after long-term abstinence (37%), fear of possible side effects (18%), recovery of spontaneous erection (15%), postponement of ED treatment because of comorbid disease treatment (11%), unwillingness to accept drug-dependent erection (7%), high drug cost (4%), unacceptability of planned sexual activity (4%), and lack of sexual interest (4%).

In a prospective study of 234 patients with mild to moderate ED who had successfully begun treatment with sildenafil 50 or 100 mg in routine clinical practice (Klotz et al 2004), 31% did not get a second prescription within 6 months of the first. Reasons for discontinuing effective sildenafil treatment in this study included lack of opportunities or desire for intercourse for 45% of patients, and partner's loss of sexual interest for 23% of cases. High treatment cost and side effects were reported as causes of abandoning treatment in 12% and 5%, respectively.

The NDC Health's Intelligent Health Repository (IHR), a databank of more than 40,000 US pharmacies, was used to identify men initiating ED treatment with one of the available PDE-5 inhibitors between November 2003 and March 2004 (Mulhall et al 2005). The frequency of medication refills, dose titration, and switching were analyzed for 146,000 men. While refill rates were significantly higher for sildenafil compared with vardenafil or tadalafil, they were low for all three inhibitors. Only 52%, 30%, and 29% refilled their prescription for sildenafil, vardenafil, and tadalafil within 6 months of initial prescription, respectively.

In a recently published study in 1036 Japanese men (Sato et al 2007), 31% failed to refill their fist prescription of sildenafil. Almost 50% of the patients dropped out at 3 years despite successful initial treatment. A lower IIEF abbreviated version (IIEF-5) score before treatment was a significant risk factor for dropout.

Higher treatment continuation rates were reported in a large prospective observational, noninterventional trial in Europe. 8047 men with ED who began (5116) or changed ED therapy as part of their routine healthcare were followed up for a period of 6 months (Hatzichristou et al 2007). In an analysis of data from treatment-naïve patients with 6 month follow-up data (4026), most continued on the same PDE-5 inhibitor throughout the study regardless of what PDE-5 inhibitor they were prescribed at baseline. Continuation rates were approximately 89% in the tadalafil cohort and 63%–64% in the sildenafil and vardenafil cohorts. Authors suggested that findings of the study should be interpreted conservatively due to its observational nature.

Conclusion

Most preference trials favor tadalafil among available PDE-5 inhibitors but have methodological flaws that allow bias introduction and limit extrapolation or results in clinical practice. Long-term adherence to PDE-5 inhibitors seems to be low despite their high efficacy, good tolerability, and ease of administration. A better understanding of factors that influence sexual behavior and thus drug utilization is mandatory in achieving patient satisfaction and compliance to treatment.

Discussion

The introduction of orally administered PDE-5 inhibitors has revolutionized the management of erectile dysfunction. The availability of several treatment alternatives should, ideally, allow patients to find the one that suits their own needs and expectations. In reality the abundance of alternatives poses the dilemma of drug choice. The lack of clinically meaningful differences in safety and efficacy of available PDE-5 inhibitors, the first-line ED treatment, makes this decision even harder.

Many studies have attempted to define patient preference and help them, as well as physicians, in their choice of treatment. Most have been presented as abstracts in various congresses and frequently study methods are inadequately

described. Only 8 have been published as full papers in peer-reviewed journals and are summarized in this review. Five of the available eight studies have assessed preference between sildenafil and tadalafil, all favoring tadalafil (chosen by 59% to 90% of patients). One combined sildenafil and vardenafil as short-acting PDE-5 inhibitors and compared them with the long-acting tadalafil, again favoring tadalafil. Vardenafil was compared with sildenafil in one trial aiming to prove noninferiority of vardenafil, only slightly favoring vardenafil. Just one of the published studies included all three PDE-5 inhibitors individually and tadalafil was once more the preferred treatment.

Data on preference is not conclusive and comparing published trials is difficult due to different patient populations and study designs. In a 2004 paper, methodological flaws of initial studies have been discussed and recommendations for minimizing bias have been proposed (Mulhall 2004). Double-blinding of drug administration, randomization of drug administration sequence, nonbiased drug administration instructions, adequately conducted crossover, comparison of equivalent drug doses for treatment periods of equal length, standardized preference assessment, declaration of patient demographics, and rigorous statistical analysis are considered important characteristics of an adequately designed and conducted preference trial. Unfortunately available studies have failed to demonstrate these characteristics (Mulhall and Montorsi 2006) thus hindering interpretation of data and extrapolation of results to clinical practice.

Reasons for preference of one drug over another have been assessed in some of the existing studies. In the majority of those, patient age group, ED etiology and severity, and in general baseline demographic characteristics were not associated with, and thus couldn't predict, preference (Ströberg et al 2003; Govier et al 2003; Eardley et al 2007). One study suggested that naïve to PDE-5 inhibitors patients may prefer short-acting inhibitors while nonnaïve may prefer the long-acting tadalafil (Ströberg et al 2006). Superiority of tadalafil in patient satisfaction and improvement in psychosocial outcomes has been suggested as a reason for preference for tadalafil (Dean et al 2006; Lee et al 2006). Other factors that may influence preference such as lifestyle issues and partner preference are not well understood. In fact partner of ED-patient preference has been assessed only in one of available studies (Lee et al 2006). Despite the preference for tadalafil (76% in the group changing treatment from sildenafil to tadalafil and 65% in the group changing from tadalafil to sildenafil) the influence of partner to patient preference and vice versa in not known. A considerable proportion of patients seem to have preferred tadalafil in trials because of its long duration of action. This can allow dissociation of drug administration from intercourse attempt making sex more spontaneous. Whether men are actually using this drug property in every-day life is a subject of debate. In an analysis of data combined from two randomized controlled trials assessing the frequency, timing and success of intercourse attempts in men with erectile dysfunction using tadalafil (Hatzichristou et al 2005), 63% of them made at least a quarter of their attempts and 42% made at least half of their attempts more than 4 hours after dose. Still, a significant number of attempts were made within 4 hours of taking the pill indicating that some connection of dosing to intercourse attempt is important even for tadalafil.

Have preference trials really helped in clinical decision making? Even though most studies show a preference for tadalafil, they have, as mentioned before, methodological flaws that allow for bias introduction. Furthermore the majority of these trials have been conducted right after launch of new PDE-5 inhibitors possibly allowing the effect of media publicity and novelty of product on preference. They have used single preference questions generating responses that are subject to contextual limitations. Another issue raised is that preference for tadalafil in trials has not been confirmed in routine clinical practice data. Prescription renewal has been used as a method of indirectly assessing patient preference and adherence as it reflects many aspects of treatment: efficacy, safety, cost considerations, and overall satisfaction from treatment experience. In a retrospective cohort study using prescription data of 2703 men initiating therapy for ED with one of the available PDE-5 inhibitors, patients who were originally prescribed sildenafil were nearly 4 times less likely to switch to another inhibitor on their second prescription compared with patients who were prescribed either tadalafil or vardenafil (Kell et al 2007). In another study mentioned above (Mulhall et al 2005) refill rates were significantly higher for sildenafil compared with vardenafil or tadalafil. Of course other studies have contradicted these results (Hatzichristou et al 2007). Prescription renewal studies have limitations including but not limited to inability to account for prescriptions that were filled but medication never used or getting the drug from alternative sources like the internet. In conclusion there is no evidence-based guidance for either clinicians or patients regarding PDE-5 inhibitor choice. This can only be made after careful patient assessment and education. Patient expectations, and broader than efficacy lifestyle factors, are important in identifying the right treatment for the right patient.

After the choice of a certain treatment has been made the question "do patients adhere to that treatment?" comes naturally. Most of the available adherence data concern sildenafil and were obtained in a period of time when this was the only PDE-5 inhibitor on the market. After vardenafil and tadalafil became available interest shifted to assessing switching between the 3 inhibitors and less is known for the adherence to the class in general. The majority of published data indicates that between 30% and 60% of initially successfully treated and satisfied men stop refilling their medication prescriptions. Diversity in study populations, duration of follow-up and methods of assessment, might account for the different results of various studies. A significant proportion of discontinuations occur within one year of treatment initiation and many men do not even fill a second prescription. Discontinuation rates are, of course, higher and abandonment of treatment occurs earlier in patients with suboptimal treatment response.

Factors that have been associated with a higher probability of discontinuing treatment include age over 60 years, the presence of comorbidities as evidenced by the use of incontinence products, insulin, or antidepressants (Souverein et al 2002) and severe ED (lower IIEF-5 scores) (Sato et al 2007). In these patients inadequate treatment response could be responsible for the higher discontinuation rates. As efficacy is very important for repeating a prescription techniques that optimize it such as adequate administration instructions and dose titration (McCullough et al 2006; Steidle et al 2007) may improve adherence. Nevertheless it is clear that efficacy is only one of the factors influencing adherence to treatment: discontinuation rates are high even if ED is successfully managed. Emotional and relationship factors play a very important role in this. Reasons for abandoning successful treatment are unmet efficacy expectations, loss of interest in sex, lack of opportunities or desire for intercourse, and partner reluctance or unwillingness. Financial reasons have also been sited as reason for discontinuation but not as often as emotional or relationship factors. Given the efficacy and safety of all available PDE-5 inhibitors, it seems that patient education and understanding of their beliefs, practices, needs and expectations is the only way to find the right treatment and improve adherence to long-term use.

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