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Review – Sexual Medicine

Evaluating Preference Trials of Oral Phosphodiesterase 5 Inhibitors for Erectile Dysfunction

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Abstract

More treatment options are available now for the treatment of erectile dysfunction (ED) than ever. Treatments include oral phosphodiesterase 5 (PDE5) inhibitors, intracavernosal injections, vacuum constriction devices, and penile implants. Clinicians, researchers, and patients are interested in making direct comparisons between the response of newer treatments and that of established and more developed therapies. Of the currently available treatment options for ED, the most commonly prescribed therapies are oral PDE5 inhibitors, which include sildenafil citrate (Viagra[®], Pfizer Inc), tadalafil (Cialis[®], Lilly ICOS), and vardenafil (Levitra[®], Bayer). However, most patient preference studies of these drugs conducted to date have serious design flaws that hinder interpretation of the data, and thus limit the utility of the results. To make an informed decision on the most appropriate treatment option available, physicians and their patients require a thorough understanding of the methodology of these studies. Clinical comparison or preference trials must establish internal and external validity if the data are to be used in a generalized patient population. We review preference studies that compared sildenafil, tadalafil, and vardenafil, and highlight study designs that can introduce bias. We propose that, like safety and efficacy trials, randomized controlled trials (RCTs) should be the gold standard for evaluating patient preference treatments for ED. We do not wish to discourage individual investigators from performing preference studies, but rather to highlight the features of current preference trials to help patients and clinicians alike become aware of potential biases from independent or industry-sponsored patient preference trials so that they can interpret the results accordingly. Key components of patient preference RCTs are reviewed: period and carryover effects, preference

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assessments, eligibility criteria, and data analysis. We discuss why these components of patient-preference RCTs are important for evaluating the validity and relevance of patient preference studies. The preference studies discussed in this brief review are summarized in Table 1, and the methodological problems with each study are indicated. We provide a recommendation for the design of such trials that can minimize bias and provide better data for physicians and their patients.

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1. Introduction

Randomized controlled trials (RCTs) are the gold standard for evaluating the safety and efficacy of new drug treatments [1,2]. A recent review highlighted several key factors to consider when interpreting safety and efficacy data from erectile dysfunction (ED) drug trials [3]. Sildenafil citrate (Viagra[®], Pfizer) [4] is the first-in-class oral drug for the treatment of erectile dysfunction (ED) and has amassed a large safety and efficacy database [5]. Two newer oral phosphodiesterase-5 (PDE5) inhibitors, vardenafil tadalafil (Cialis[®], Lilly ICOS) [6] and (Levitra[®], Bayer), [7] both of which have an identical mechanism of action to that of sildenafil, have recently become available for the treatment of ED. However, there are more than 4 times the number of clinical trials published for sildenafil than for vardenafil and tadalafil [5]. Clinicians, researchers, and patients are interested in making direct comparisons between the clinical efficacy and safety of the 3 available PDE5 inhibitors. However, The Erectile Dysfunction Guideline Update Panel of the American Urological Association states that it is not valid to compare the treatment response and tolerability of these agents based on results from improperly designed and conducted comparative studies [8]. In addition, a shift from safety and efficacy studies to patient preference studies requires an understanding of the unique factors that can influence interpretation of the results [9]. To make an informed decision on the most appropriate treatment option available, physicians require a thorough understanding of the methodology of these studies. Clinical comparison or preference trials must establish internal and external validity if the data are to be used in a generalized patient population (Table 1).

A clinical trial has internal validity and generalized relevance when the extent of systematic error—biases and confounding—is minimized. However, even within the RCT paradigm, subtle differences in trial design, or the reporting thereof, can affect outcomes [1,2,10]. In particular, study design, eligibility criteria, demographic characteristics of the

study population, outcome measures, and analytic techniques may differ across studies resulting in noncomparability of the results. Within the many available RCT designs, the crossover study, in which patients serve as their own controls, is the best trial design capable of measuring patient preference. Crossover drug trials have the advantages of the ability to expose patients to multiple medications and requiring fewer patients than parallel studies would necessitate. A well-designed crossover study for patient preference analysis should involve patients being randomized to different sequences of drug administration (ABC, CAB, BAC, etc) to guard against potential bias introduced at a given period, or carried over from 1 period to the next.

2. Period and carryover effects

A period effect occurs when there are evolving symptoms or an adaptation period to treatment, independent of drug order, such that the results of later treatment periods are dependent, at least in part, on the results of earlier periods [11]. The PDE5 inhibitors may be susceptible to period effects; the probability of achieving sexual intercourse success with sildenafil increases with increasing number of attempts, up to approximately 8 attempts, and 54%–58% of men who are not initially successful with sildenafil can become successful after reeducation and counselling [12–14]. Period effects may be especially relevant for preference assessment trials of PDE5 inhibitors, given that many treatment periods within RCTs are 8–12 weeks in duration. Treatment period lengths of different duration may falsely assign preference. For example, Stroberg et al., enrolled men with ED who were using sildenafil and concluded that a majority of men preferred tadalafil after 9 weeks of open-label treatment, compared with sildenafil, which was given for only 3 weeks [15]. The inclusion of only current sildenafil users may have also prebiased the results in favor of the comparator (discussed below). Period effects can also be observed in unblinded

Table 1 – Patient preference trials of phosphodiesterase 5 inhibitors

Author	PDE5 Inhibitors	Results	Methodological concern	Ref.
Ströberg et al.	sildenafil, tadalafil	patients preferred tadalafil to sildenafil 9:1	1-way crossover, open-label, unequal treatment periods, dissimilar dosing instructions, nonequivalent dosages, study conducted soon after availability of tadalafil in Europe, all participants were white	[15]
Porst et al.	sildenafil, tadalafil, vardenafil	45% preferred tadalafil, 30% preferred vardenafil, 12% preferred sildenafil, 12% had no preference	open-label, drug order not known, period and carryover effects, preconceived treatment attributes, EF-domain scores were similar between groups	[19]
Ströberg et al.	sildenafil, tadalafil, vardenafil	Overall, 53% preferred tadalafil, 25% preferred sildenafil, 15% preferred vardenafil	1-way crossover, open-label, unequal treatment periods, dissimilar dosing instructions, twice as many doses (8) of tadalafil than sildenafil (4) or vardenafil (4), single preference assessment at end of study, no difference in treatment preference among PDE5-naïve patients (35% preferred tadalafil, 33% preferred sildenafil, 23% preferred vardenafil)	[20]
Von Keitz et al.	sildenafil, tadalafil	73% preferred tadalafil	nonequivalent dosages, dissimilar dosing instructions, higher doses limited to 35% of patients taking sildenafil, treatment attributes provided, patients given tadalafil were provided extra suggestions on how and when to take it to increase efficacy and satisfaction	[21]
Govier et al.	sildenafil, tadalafil	66% preferred tadalafil	nonequivalent dosages, dissimilar dosing instructions, fixed-dose, treatment attributes provided	[22]
McMahon et al.	sildenafil, tadalafil	Overall, 82% preferred tadalafil. At highest dose, patients preferred sildenafil	open-label, post-hoc analysis, patients were switched from sildenafil to tadalafil, questionnaire tailored for tadalafil preference	[24]
Park et al.	sildenafil, tadalafil, vardenafil	55% preferred sildenafil, 25% preferred vardenafil, 19% preferred tadalafil	study design unclear, small patient group	[25]
Somer et al.	sildenafil, tadalafil, vardenafil	At max dose, 50% preferred vardenafil, 31% preferred sildenafil, 19% preferred tadalafil	study conducted soon after availability of vardenafil in Europe, efficacy was similar for all three PDE5 inhibitors, determination of patient preference not clear	[29]
Claes and Van Poppel	sildenafil, tadalafil, vardenafil	36% preferred vardenafil, 32% preferred sildenafil, 32% preferred tadalafil	open-label, drug dose and order not known	[30]

crossover trials of non-PDE5 inhibitors for the treatment of ED [16]. One of the first preference trials in men with ED was an open-label trial that assessed the preference for sildenafil in men who had been successfully treated with intracavernosal injection (ICI) therapy for ≥ 6 months [17]. Blinding to treatment was not possible in this study, which may have prebiased patients in favor of the less invasive oral therapy. The observed period effect across treatments may be due to improved erectile function, sexual intercourse success, and increased confidence with sexual performance during the study, [16,18] suggesting that the treatment of ED may be particularly vulnerable to this type of bias.

A carryover effect has its origin in a preceding treatment and is thus order dependent: The effect of the first treatment used may carry over to the next treatment, making the second treatment seem more effective than the first [11]. Carryover effects can

significantly affect data interpretation of crossover drug trials in which a single drug sequence is used, which may make later drugs appear more effective than former drugs (Fig. 1). This type of bias may be especially true of the oral PDE5 inhibitors, due in part to their similar mechanisms of action, that patients may become increasingly comfortable with use, and preconceived perceptions about individual study medications may further add to the preference bias. An open-label crossover trial of all 3 PDE5 inhibitors found that tadalafil was preferred by more men [19]. However, treatment preference may have been increased by the cumulative increased confidence and success with sildenafil and vardenafil in earlier treatment periods. Additionally, it is possible that these effects are compounded by preconceived treatment attributes of tadalafil. This is especially true in unblinded studies, in which patients and investigators know which medication is being taken

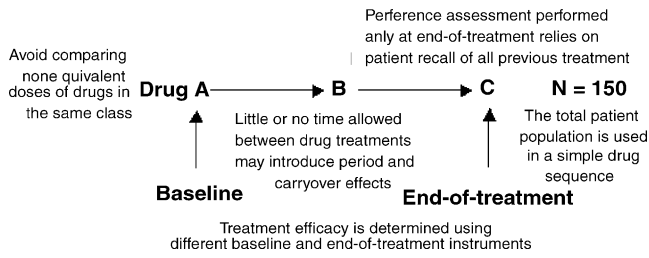


Fig. 1 – One-way crossover trials of drugs may introduce several biases, as well as period and carryover effects.

during each period. The aforementioned study demonstrates that the drug sequence order can introduce known, as well as unforeseen bias, including carryover and period effects, which can significantly affect results.

2.1. Equivalent dosing, timing, and instruction

In addition to bias introduced by the sequence of study drugs, the amount of time allotted for each medication, [15] the amount of study drug, [20] the dose of study drug, [21,22] and the instructions that accompany each drug can influence the results [15,21,22]. As discussed earlier, in an open-label, 1-way crossover study, patients were exposed to sildenafil and tadalafil for unequal periods, and they preferred the drug provided in the longer period [15]. Similarly, in another preference trial, patients were prescribed twice as many tadalafil tablets as sildenafil or vardenafil tablets, they received verbal and written information regarding the onset of action and duration of action specific to each treatment, and they were provided a single drug sequence [20]. Patients were instructed to finish all 4 doses of sildenafil first (no more than once daily), then finish all 4 doses of vardenafil (no more than once daily), and finish the treatment sequence with the 8 provided doses of tadalafil (no more than once daily). In this particular study, preference for tadalafil may have been predetermined by investigators. The sequence order, greater exposure to tadalafil (twice as many pills), and information regarding duration of action likely pre-biased patients toward the last drug tried. Interestingly, of the PDE5 inhibitor naïve patients who responded to medication, preference for each of the 3 drugs was roughly equal (33% for sildenafil, 23% for vardenafil, and 35% for tadalafil) [20].

In 2 other reports, each of a multicenter, randomized, double-blind, crossover nature, patient preference was determined after patients were given the maximal dosage of tadalafil versus the half-maximal dosage of sildenafil [21,22]. The max-

imal dose of drug (tadalafil) was preferred to the half-maximum dose medication (sildenafil) by 73% [21] and 66% [22] respectively, which was likely due in large part to the increased efficacy with the maximum dose. This is supported by the results of a pooled analysis of flexible-dose, placebo-controlled, double-blind studies of sildenafil [23]. In this analysis, men with ED preferred the increased efficacy of the maximal dose of drug [23]. In addition, when patients with ED who had been taking sildenafil (25, 50, or 100 mg) were crossed over to tadalafil (20 mg), the patients who had been taking the highest dose of each drug expressed a preference for sildenafil [24]. Similarly, when patient preference to both half-maximum and maximal doses were compared in an open-label preference study of all 3 PDE5 inhibitors, the majority of men (58%) preferred sildenafil (27% for vardenafil and 15% for tadalafil) [25].

The difference in patient preference for one PDE5 inhibitor over another can be easily influenced by the study design. In general, patients are more likely to remember and prefer the highest effective dose, the dose that they have used longest, or their most recent treatment. Preference would be almost assured if, for example, the most recent treatment was at maximal dose for efficacy and lasted 3 times longer than a previous treatment at half-maximum dose. In such a case, it would be inappropriate to conclude that patients preferred one treatment to another.

A properly designed and executed double-blind, randomized, crossover trial is the only design capable of appropriately measuring patient preference and can dramatically reduce bias if the study is appropriately designed (Fig. 2). For example, the trial involving all 3 oral PDE5 inhibitors described above [19] could have easily been converted to a RCT design with proper blinding to the drug sequence in order to generate a more powerful multi sequence

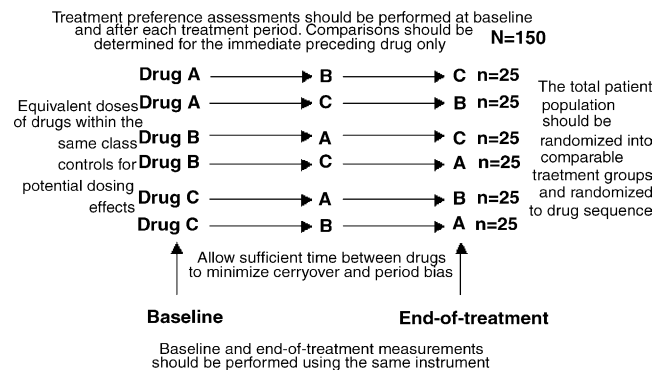


Fig. 2 – Well designed crossover drug trials can minimize bias and period or carryover effects.

crossover trial with more relevant results. An equal amount of time should be allowed for each drug, equivalent drug dosages should be used, and sufficient time should be allotted between drug treatments for adequate washout of any previous period or carryover effects. Moreover, drug preference assessments should not wait until the end of the study, rather they should be performed as soon as 2 treatments have been taken.

2.2. Preference assessment

A relatively simple outcome, such as preference, can be variably defined, which makes it difficult to compare preference results between studies. Some preference trials have used a single treatment preference question (TPQ), which simply asks “Which treatment did you prefer?” or a global efficacy assessment (QEA) or question (GEQ), such as, “Did the medication you were taking improve your erections [22,26–28]?” However, responses to a single preference question are contextually limited and lack robustness. Other studies have used a multi question preference questionnaire, including questions regarding time to onset, duration of action, hardness, and side effects [19,29]. In this case, preference is defined in 2 ways; (1) a preference for certain treatment attributes, and (2) a comparative preference of one treatment over another. For example, in the German Men’s Health Study Group comparison trial of all 3 oral PDE5 inhibitors, there was no clear choice for ease of getting an erection, duration of erection, or hardness of erection, but 60% of men preferred sildenafil for fewer side-effects (vs 40% for vardenafil and tadalafil) [29]. However, the authors reported that tadalafil and vardenafil were preferred to sildenafil for overall preference. This study was performed a few months after the launch of vardenafil and tadalafil. Thus, with similar efficacy to sildenafil, but with more safety issues, it is conceivable that men may have preferred the 2 newer PDE5 inhibitors because of their novelty on the market. Two more recent studies found no significant preference for one PDE5 inhibitor over another in 66 PDE5 inhibitor-naïve men with ED, [20] and in 418 PDE5 inhibitor-naïve men with ED [30]. However, when subdivided according to age, etiology, and severity of disease, younger men with mild ED of psychogenic origin preferred tadalafil for duration of action, whereas older men with moderate or severe ED of organic origin preferred sildenafil or vardenafil for efficacy and fewer adverse events [20,30]. Clearly a single question, such as the TPQ or GEA, could not elucidate subtle differences between patients, and

their preference for certain treatment attributes. Furthermore, patients motivated to participate in preference trials, particularly if they are not PDE5 inhibitor naïve, may already be biased in favor of the comparator agent.

Other studies have relied on functional efficacy assessments to determine patient preference. These include patient-kept diaries, that record the ability to achieve vaginal penetration (SEP2), [31] or the International Index of Erectile Function (IIEF), [32] the Sexual Health Inventory for Men (SHIM), [33] or treatment satisfaction scores on the Erectile Dysfunction Index of Treatment Satisfaction (EDITS) [34]. However, it is inappropriate to equate drug preference with treatment efficacy or satisfaction scores alone. For example, intracavernosal injections and vacuum devices are effective in achieving erections in most patients, but patients generally prefer the less invasive and easier-to-use oral PDE5 inhibitors [35,36]. The attributes of an ED treatment that patients prefer should be considered with the treatment’s efficacy to help determine the most favorable treatment option for patients. Results from the MALES (Men’s Attitudes on Life Events and Sexuality) study reveal that of the 694 men with ED, 39% preferred a treatment that is reliable, and 31% and 26% preferred a therapy that is tolerable and safe, respectively [37]. Only 8% and 9% reported that long duration of action or rapid onset, respectively, was important. A robust questionnaire that highlights efficacy, safety, and reasons for preference of one PDE5 over another would better help clinicians provide the best treatment option for patients to achieve consistently hard erections for satisfying sexual intercourse.

2.3. Eligibility criteria

In all clinical trials, researchers attempt to select patients who are representative of the population being tested. In ED clinical trials, the core set of exclusion criteria often includes patients with hypogonadism, uncontrolled hypertension or diabetes, Peyronie’s disease, severe psychiatric disorders, and unstable cardiovascular disease that would render sexual activity inadvisable. Because they are applied before randomization, eligibility criteria do not affect the internal validity of the trial [2]. However, if results across trials are compared, to establish external validity, the eligibility criteria should be described in sufficient detail to adequately define the patient population.

Some eligibility criteria are designed to increase the likelihood of a favorable outcome, which may significantly alter the patient-reported preference of

PDE5 inhibitors. For example, investigators comparing sildenafil to the newer drugs have included patients who had been previously treated successfully with sildenafil, but have excluded treatment nonresponders or patients who had experienced unacceptable side effects [15,31,38]. These studies enriched the population of likely treatment responders, and reduced the likelihood of adverse events, which results in overestimating the efficacy of the newer drugs and underestimating the side effects that are likely to be observed when the drug is used in a broader clinical population. By excluding treatment nonresponders from preference trials involving the newer ED drugs, it is likely that patients with more severe ED are also excluded. This produces artificially higher efficacy rates of treatment satisfaction than those previously reported for trials that included patients with mild-to-moderate and severe ED or those who were PDE5 inhibitor naïve. This approach may result in misleading preference statements. Trials that included only treatment responders, by excluding nonresponders, were likely not compromised with respect to internal validity, because the randomization of patients to treatment groups reduces this possibility, but the external validity and generalizability is questionable [2]. In addition, men committing to a preference trial who have previously used sildenafil may in fact be enrolling in the “new” drug trial because of some real or perceived difficulty they had in integrating sildenafil into their sexual life. Enrolling men who are currently dissatisfied with their current treatment biases them in favor of the “new” drug. Similar to the inclusion of only sildenafil responders in a preference trial, inclusion of men who are dissatisfied with their current treatment produces artificially higher preference rates. Results from trials of this nature cannot be compared with results from other drug trials that included treatment nonresponders, from trials of treatment-naïve patients, or from trials in which preference with current treatment is taken into account.

2.4. Data analysis

The statistical analysis should consist of fundamental elements including delineation of *a priori* covariate and/or subgroup analyses [2]. All preference data should be analyzed using the intent-to-treat (ITT) principle with the last observation carried forward (LOCF). This should be a predetermined set of criteria that minimizes potential biases and loss of statistical power that can result from nonrandom study attrition [39,40]. For example, if withdrawals

or discontinuations are the result of a treatment effect, analyses that include only study completers will overestimate treatment preference. It is likely that patients who withdrew from a study differ in some systematic way from those who did not [2,39]. If the discontinuation rate is high, this factor can seriously affect the outcome of the study. To reduce these potential biases, all randomized patients should be included in the preference analysis according to their original group assignment, regardless of their adherence to the study protocol [40].

3. Conclusions

The introduction of easy to use, oral PDE5 inhibitors has revolutionized the treatment and management of ED. Patients have more choices than ever before, and therapy can be better tailored to a patient’s and his partner’s attitudes toward sex and their ED therapy use patterns. Moreover, the heightened awareness of ED as a potential indicator of underlying vascular disease has stimulated discussion between patients and clinicians about cardiovascular health. As clinicians, researchers, and patients try to understand the difference between the ED treatment options available, it is important to discuss the results of patient preference studies in context with the study methodology and potential bias that may influence the results. In addition to the excellent safety and efficacy profile of PDE5 inhibitors, it is important for clinicians to provide an accurate and balanced assessment of treatment attributes for patients and their partners to make an informed decision on their preferred therapy.

Other concepts of patient preference studies that help minimize bias, but were not covered in this brief review, are included in Table 2. There is potential for the introduction of investigator bias that may influence the design or interpretation of preference trials. Although case series and cohort study designs are useful for generating hypotheses, the crossover RCT design is the most definitive method for evaluating the efficacy and preference of new drug treatments for ED. Even so, any single patient preference trial must be scrutinized for internal validity and external generalizability. Internal and external validity must be demonstrated, particularly if the results are to be compared across studies or with other patient populations. In addition to RCTs that are properly designed and executed, the clinical characteristics of ED treatments should be considered to help determine the most favorable treatment option for patients. The

Table 2 – Attributes of a well designed preference trial that minimizes bias, versus a poorly designed preference trial that likely introduces bias

Minimizes bias	Potential for extensive bias
<ul style="list-style-type: none"> • Crossover design • Randomized patients • Double-blind • Does not eliminate previous nonresponders or includes only treatment naïve patients • Randomized drug sequences • Equivalent drug doses used • Sufficient washout time between drugs • Baseline and end-of-each treatment efficacy determined using the same instrument • Treatment preference assessment after each comparison group period • Treatment periods of equal length • Preference assessment is not biased toward a particular drug • Neutral consent form • Data analysis on intent to treat group 	<ul style="list-style-type: none"> • Non crossover design • Patients not randomised • Open-label • Excludes non-responders with previous experience with one or more of the study drugs • Single drug sequence • Non-equivalent doses of study drugs used • Little or no time between drugs • Baseline and end-of-treatment efficacy determined using different instruments • End-of-treatment preference assessment only • Treatment periods of different lengths • Preference assessment favors one drug • Biased consent form • Data analysis on period completers

results of such studies will provide useful information to help guide evidence-based practice and improve patient outcomes.

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