

A Multicenter, Randomized, Double-Blind, Crossover Study to Evaluate Patient Preference between Tadalafil and Sildenafil

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Abstract

Purpose: To assess patient preference for erectile dysfunction treatment between either sildenafil or tadalafil, each administered with their respective dosing instructions, and to evaluate preference for either sildenafil or tadalafil dosing instructions during tadalafil therapy.

Methods: We conducted a randomized, double-blind, crossover study consisting of four treatment arms. Because the dosing instructions for sildenafil and tadalafil are different, a unique methodology using sham placebo arms was employed to maintain the blind. To assess drug preference, 219 patients were randomized to either sildenafil 50 mg or tadalafil 20 mg, with dosing instructions reflecting their respective product profiles. To assess dosing instruction preference during tadalafil therapy, 46 patients were randomized to tadalafil 20 mg with either tadalafil or sildenafil dosing instructions. After 12 weeks, patients were crossed-over. After 4 weeks of each treatment, all patients following sildenafil dosing instructions were offered the opportunity for an upward dose titration. In a double-blind fashion, all patients who requested an upward titration received additional capsules. To mimic the pattern of dose usage observed in clinical practice, the number of patients who received additional double-blind active medication was limited to 35% of patients taking sildenafil in each treatment period in each country. Following the crossover treatment period, patients chose their preferred double-blind treatment with dosing instructions to receive in the 12-week extension period.

Results: In the drug preference assessment, 132 of 181 (73%) evaluable patients chose to receive tadalafil ($p < 0.001$) during the extension period. In the dosing instruction preference assessment, 24 of 36 (67%) evaluable patients preferred tadalafil with tadalafil dosing instructions ($p = 0.046$). Sildenafil and tadalafil were well tolerated.

Conclusions: In the doses utilized in this study, 73% of patients preferred tadalafil with tadalafil dosing instructions for the treatment of their erectile dysfunction over sildenafil with sildenafil dosing instructions. During tadalafil therapy, 67% of patients preferred tadalafil dosing instructions over sildenafil dosing instructions.

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1. Introduction

In the era of shared decision making between patients and clinicians and the formal research evaluation of outcomes, the formal assessment of patient

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preference for treatments is increasing in importance [1]. Erectile dysfunction (ED), afflicts approximately 152 million men worldwide [2] and is a distressing and disabling condition that impairs interpersonal relationships, self-esteem, and quality of life [3–6]. Despite the availability of devices and pharmaceutical agents to treat this distressing condition, only a few preference assessment studies have compared ED treatment modalities [7,8]. Additionally, no preference assessment study comparing the more recently introduced PDE-5 inhibitors has been published. We report the methodology and results of a preference study that in a novel blinded fashion compared sildenafil and tadalafil, two oral PDE-5 inhibitors with different pharmacokinetic profiles and different instructions for use.

Sildenafil (Viagra[®], Pfizer), introduced in 1998, has demonstrated efficacy in the treatment of ED. For example, after 12 weeks of treatment, 74% of men reported improved erections with sildenafil compared to 19% of placebo-treated patients [9]. Twenty percent to 50% of patients, however, who respond to sildenafil nevertheless discontinue its use [10]. These data suggest that the treatment needs for many men with ED remain unmet.

Tadalafil (Cialis[®]; Lilly ICOS LLC), approved as an oral ED therapy in 2002, possesses pharmacokinetic properties that are quite different from sildenafil. The half-life for sildenafil is approximately 4 hours [11] compared to 17.5 hours for tadalafil [6]. In addition, tadalafil may be taken without regard to food while sildenafil bioavailability may be decreased by a fatty meal. Furthermore, some men with ED treated with tadalafil have achieved successful intercourse as early as 16 minutes and up to 36 hours after dosing [12–14]. Similar to sildenafil, in a clinical trial of American men, 79% of patients treated with tadalafil reported improved erections after 12 weeks of treatment compared to 19% of patients treated with placebo [15].

In clinical trials of ED therapy, efficacy is usually measured by the International Index of Erectile Function (IIEF) [16] and by Sexual Encounter Profile (SEP) diaries. The IIEF is a multi-dimensional scale measuring erectile function, orgasmic function, sexual desire, intercourse satisfaction, and overall satisfaction over a 4-week period [16]. The SEP diaries are completed after each sexual intercourse attempt and measure the patient's ability to penetrate and to complete sexual intercourse. These efficacy measures, however, do not assess all aspects of sexual experience or patient preference.

Medical management of ED is now goal-oriented, considering patient preference and needs, rather than being based solely on etiology [7]. As the number of

safe and efficacious treatment options continues to grow, patient preference will be further emphasized in treatment decisions. Studies investigating patient preference for ED treatment are therefore needed to supplement studies with traditional efficacy measurement scales.

We therefore conducted a study to assess patient preference between sildenafil and tadalafil. The purpose of this study was two-fold: (1) to assess patient preference for ED treatment between either sildenafil or tadalafil, each administered with their respective dosing instructions and (2) to evaluate preference for either tadalafil or sildenafil dosing instructions during tadalafil therapy.

2. Patients and methods

2.1. Patients

Men 18 to 65 years of age, who were in a sexual relationship with a female partner, and who had at least a 3-month history of ED were eligible for inclusion. ED was defined as a consistent change in the quality of erection that adversely affected the patient's satisfaction with sexual intercourse. Eligible patients agreed not to use another form of ED treatment during the entirety of the study, including the Screening, Crossover Treatment, and Extension Periods, and for 96 hours after the conclusion of the Extension Period. Patients who were non-responsive to previous sildenafil treatment were allowed to enter the study.

Patients with rapid ejaculation, ED due to an untreated endocrine disorder (e.g., hypopituitarism, hypothyroidism, or hypogonadism), a history of pelvic surgery without evidence of preserved erectile function, stroke or spinal cord injury within the preceding 6 months, history of HIV infection, current treatment with nitrates, myocardial infarction within the preceding 90 days, coronary revascularization within the preceding 90 days, or history of unstable angina within the preceding 6 months were excluded from the study. Additionally, patients with retinitis pigmentosa were excluded as this is a labeled caution against sildenafil use [11].

2.2. Methods

This randomized, double-blind, two-period crossover study was conducted at 15 sites in the United States, Germany, and Spain between January and September 2002. The study was conducted in accordance with the ethical principles from the Declaration of Helsinki and in conformity with the applicable laws and regulations of each country. Ethical review boards (ERBs) reviewed and approved the protocol for each site. All study participants provided written informed consent.

2.3. Study design

The Drug Preference Assessment measured the study's primary objective, patient preference for sildenafil, at a starting dose of 50 mg, or tadalafil 20 mg. Sildenafil and tadalafil were administered with their respective dosing instructions. In the Dosing Instruction Preference Assessment, all patients received tadalafil 20 mg and their preference for either sildenafil or tadalafil dosing instructions was measured. The Dosing Instruction Preference Assessment was designed to determine if patients prefer the flexibility of sexual

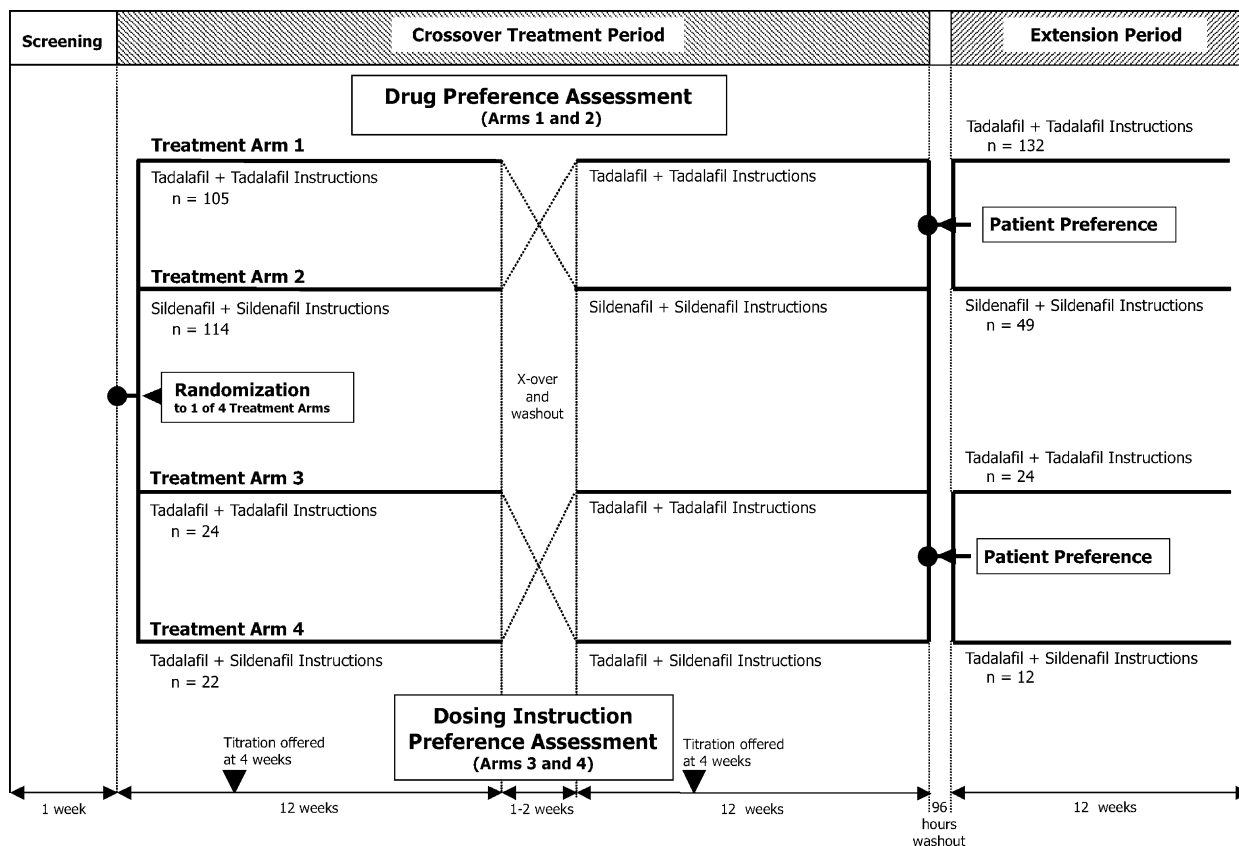


Fig. 1. Study design illustrating treatment periods.

relations up to 24 hours post-dose versus a 4-hour window post-dose. The sildenafil label instructs men with ED to take the drug 1 hour prior to anticipated sexual relations, but indicate that the drug is effective 30 minutes to 4 hours post-dose. In contrast, the increased duration of effectiveness for tadalafil was incorporated into dosing instructions used in this study (discussed below).

During both the Crossover Treatment Period and the Extension Period (Fig. 1), patients recorded the date and time they took study drug in a medication diary and the date and time for sexual intercourse attempts in a sexual encounter diary.

2.4. Treatment arms and blinding

The protocol provided to investigators stated that after a treatment-free screening period of approximately one week, patients would be randomly allocated to receive tadalafil 20 mg (with either sildenafil or tadalafil dosing instructions), sildenafil 50 mg (with sildenafil dosing instructions only), or placebo (with either sildenafil or tadalafil dosing instructions). The protocol also stated that patients would receive active treatment in at least one of the phases of the Crossover Treatment Period.

In fact, no patient received placebo. Patients were randomly allocated to either the Drug Preference Assessment (Treatment Arm 1, tadalafil 20 mg–sildenafil 50 mg or Treatment Arm 2, sildenafil 50 mg–tadalafil 20 mg) or the Dosing Instruction Preference Assessment for tadalafil therapy (Treatment Arm 3, tadalafil dosing instructions–sildenafil dosing instructions or Treatment Arm 4, sildenafil dosing instructions–tadalafil dosing instructions). Information about the true treatment arms was provided exclusively to each ERB as a protocol supplement.

The sham placebo arms represent a unique methodology to mask treatment allocation when two different dosing instructions for two drugs with different pharmacokinetic profiles are used. Patients receiving sildenafil received only sildenafil dosing instructions, whereas patients receiving tadalafil received either sildenafil or tadalafil dosing instructions. Without the sham placebo arms, the receipt of tadalafil dosing instructions would have unblinded the patients and their physicians. The sham placebo arms created in the minds of both patients and their physicians the possibility that the patient could receive placebo with either sildenafil or tadalafil dosing instructions. Thus, the dosing instructions did not unblind the patients or their physicians as to the treatment allocation. The patients and treating physicians remained blinded in the Extension Period. Furthermore, the sildenafil and tadalafil study drugs were identically encapsulated to help ensure blinding. The encapsulation did not significantly impact the dissolution of the two drugs.

2.5. Dosing instructions

The sildenafil dosing instructions were based on the manufacturer-provided instructions [11] and were provided to maximize the efficacy of sildenafil (Fig. 2). The tadalafil dosing instructions (Fig. 2) were derived from instructions used in previous tadalafil clinical trials and model language developed for patients. The tadalafil dosing instructions were also the prototypes for future educational materials for initiating tadalafil therapy.

In both the Drug Preference Assessment and the Dosing Instruction Preference Assessment, all patients following sildenafil dosing instructions had an option to increase their dose after 4 weeks of treatment. In double-blind fashion, all patients who requested an

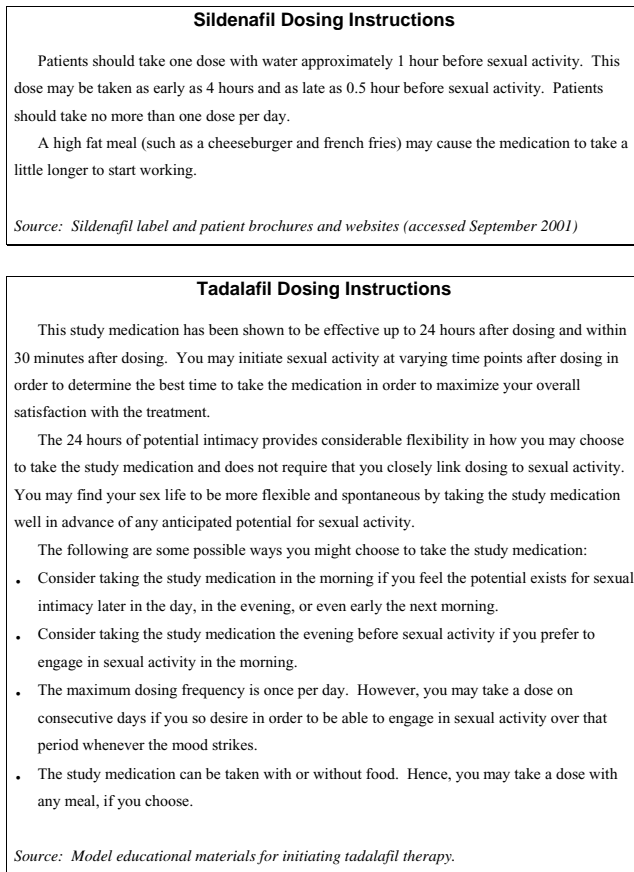


Fig. 2. Dosing instructions.

upward titration received additional capsules. The number of patients who received additional double-blind active medication was limited to 35% of patients taking sildenafil in each treatment period in each country. The remaining sildenafil patients and all the tadalafil patients who requested titration received double-blind placebo. The limit on the number of patients treated with sildenafil who could titrate was imposed in order to mimic the pattern of dose usage observed in clinical practice (i.e., an estimate based on available data of the proportion of sildenafil users who actually upwardly titrate their dose) [17–19]. Because titration was not possible for patients taking tadalafil with sildenafil dosing instructions, patients and investigators remained blinded through the use of placebo for upward titration.

At the conclusion of the Crossover Treatment Period, patients elected to continue in the study's 12-week Extension Period and selected the double-blind treatment they preferred to receive. Both study drugs were provided at no charge to the patients to remove acquisition cost as a variable in determining preference. The Extension Period was preceded by a 96-hour washout period.

2.6. Outcomes and assessments

The primary outcome was patient preference for ED treatment, as assessed by blinded patient choice between either sildenafil or tadalafil, administered with their respective dosing instructions, to receive in the Extension Period. Secondary outcomes included patient preference for either tadalafil or sildenafil dosing instructions during tadalafil therapy and the time between dosing and sexual attempt.

Safety assessments included a complete patient medical history, physical examination, 12-lead electrocardiogram, and standard serum chemistry and hematology tests at the screening visit. Blood pressure, pulse, and the incidence of adverse events were recorded at every clinic visit. Adverse events were summarized by the Medical Dictionary for Regulatory Activities (MedDRA version 4.0) for severity and relationship to study drug.

2.7. Statistical analyses

A sample size of 200 patients randomized to the Drug Preference Assessment was estimated to achieve 80% power for rejection of the null hypothesis that the proportion of patients choosing sildenafil or tadalafil at the beginning of the Extension Period would be equal, assuming 90% of patients would continue into the Extension Period and approximately 60% of these patients would choose tadalafil. A sample size of 40 patients for the Dosing Instruction Preference Assessment was considered sufficient to measure patient preference for either sildenafil or tadalafil dosing instructions during tadalafil therapy.

Preference analyses included all patients who continued into the Extension Period and chose to continue receiving an ED treatment. A two-tailed z-test was used to test the null hypothesis of equal treatment preference. Significance at the 0.05 level was required to reject the null hypothesis. To compare the time distribution between dosing and sexual attempt, a linear mixed model was used with the log of the mean time as the response variable, fixed terms for treatment and period, and a random term for patients. Safety analyses included a summary of adverse events by treatment for all randomized patients. All other analyses presented are *post hoc* analyses.

3. Results

3.1. Demographics and disposition

Of the 299 men screened (72 from Germany, 84 from Spain, and 143 from the US), 265 were eligible to enroll and 219 were randomly allocated to the Drug Preference Assessment (Treatment Arm 1, $n = 105$; Treatment Arm 2, $n = 114$). In the Dosing Instruction Preference Assessment, 46 were randomly allocated (Treatment Arm 3, $n = 24$; Treatment Arm 4, $n = 22$).

Ultimately, 181 (83%) patients in the Drug Preference Assessment and 36 (78%) patients in the Dosing Instruction Preference Assessment chose to continue a double-blind treatment in the Extension Period (Figs. 1 and 3). Only two patients, one each for sildenafil and tadalafil, discontinued due to perceived lack of efficacy.

Patient baseline characteristics were similar across the treatment sequences ($p > 0.05$). The mean age of the patients was 53 and ranged from 21 to 65 years (Table 1). Most patients in the sample were Caucasian (89%), had moderate or severe ED (82%) of organic or mixed etiology (93%) and suffered from ED for one year or more (94%). The majority of patients (66%) had used sildenafil prior to the study, and 29% of the patients were current smokers. Twenty-six percent of the patients had pre-existing hypertension at baseline.

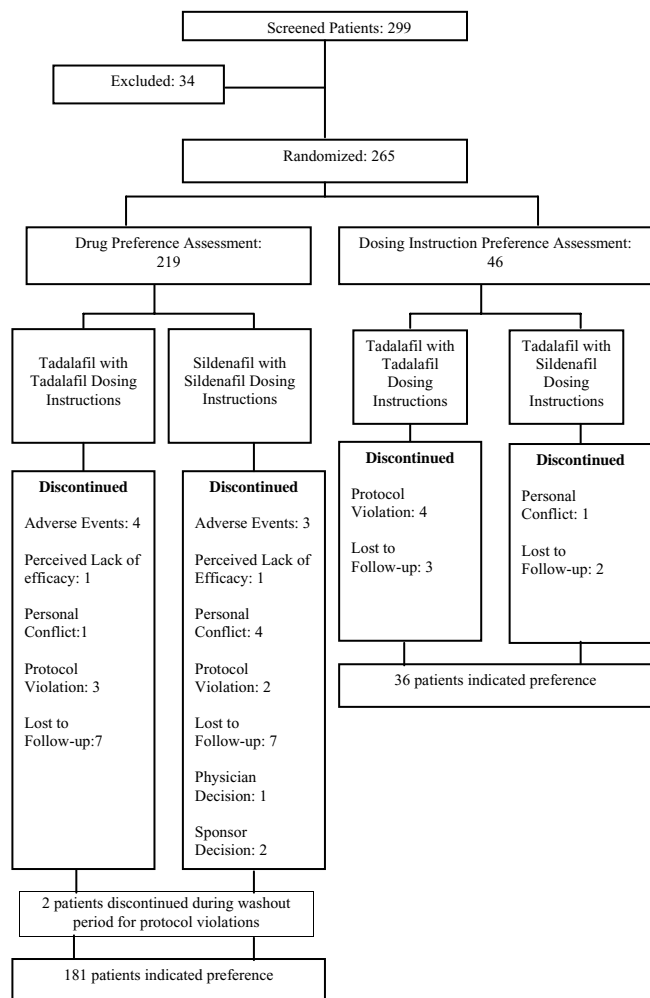


Fig. 3. Patient progress through the study.

3.2. Drug preference

Of the 181 patients in the Drug Preference Assessment who chose a double-blind ED treatment for the Extension Period, 132 (73%) preferred tadalafil and 49 (27%) preferred sildenafil ($p < 0.001$) (Fig. 4a).

At least 70% of patients in all age categories (less than 50 years, 76%; between 50 and 60 years, 70%; and over 60 years, 73%) preferred tadalafil over sildenafil ($p < 0.005$ in all categories). Likewise, approximately 70% of men in Spain and in Germany preferred tadalafil over sildenafil ($p = 0.003$ and $p = 0.004$, respectively); 78% of US men preferred tadalafil ($p < 0.001$). The existence of comorbidities among patients did not alter preference; 87% of patients with diabetes and 79% of patients with hypertension preferred tadalafil over sildenafil ($p < 0.001$ for each, Fig. 4b).

Most patients with ED of organic (73%, $p < 0.001$) or mixed origin (76%, $p < 0.001$) preferred tadalafil over sildenafil. For patients with ED of psychogenic origin, the number of patients was small ($n = 10$) and

Table 1
Baseline patient characteristics^a

Characteristic	All patients ($N = 265$) ^b
Mean age: year (range)	52.5 ± 9.3 (21–65)
Race/ethnicity	
Caucasian	235 (89)
African-descent	19 (7)
Hispanic	5 (2)
Asian	6 (2)
ED severity ^c	
Mild	48 (18)
Moderate	149 (56)
Severe	68 (26)
ED etiology ^c	
Organic	112 (42)
Psychogenic	18 (7)
Mixed	135 (51)
ED duration	
<1 year	16 (6)
≥1 year	249 (94)
Previous sildenafil therapy	174 (66)
Current smoker	78 (29)
Comorbid conditions	
Hypertension	68 (26)
Diabetes mellitus	44 (17)
Depression	10 (4)
Coronary artery disease	9 (3)

^a Data are given as either mean ± S.D. or number (%).

^b No differences in baseline patient characteristics were observed among the four treatment sequences ($p > 0.05$).

^c According to each investigator's clinical judgment.

equal numbers of patients preferred tadalafil and sildenafil. A 3 to 1 margin of preference for tadalafil over sildenafil was observed in men with mild or moderate ED ($p = 0.003$ and $p < 0.001$, respectively). A 1.8 to 1 margin of preference for tadalafil over sildenafil was noted among men with severe ED ($p = 0.058$).

The order in which the treatments were received did not affect preference; 67% and 78% of patients in Treatment Arms 1 and 2, respectively, preferred tadalafil over sildenafil ($p < 0.001$ in both treatment arms). Patients who used sildenafil prior to the study or patients who were sildenafil naïve both preferred tadalafil over sildenafil (71% and 76%, respectively, $p < 0.001$, Fig. 4c).

Similarly, titration did not alter patient preference for tadalafil. While taking sildenafil 50 mg, 58% of patients in Treatment Arm 1 and 48% of patients in Treatment Arm 2 requested titration ($p = 0.026$). Thirty-five percent and 34% of patients randomized to Treatment Arm 1 and Treatment Arm 2, respectively, had their titration request actually granted

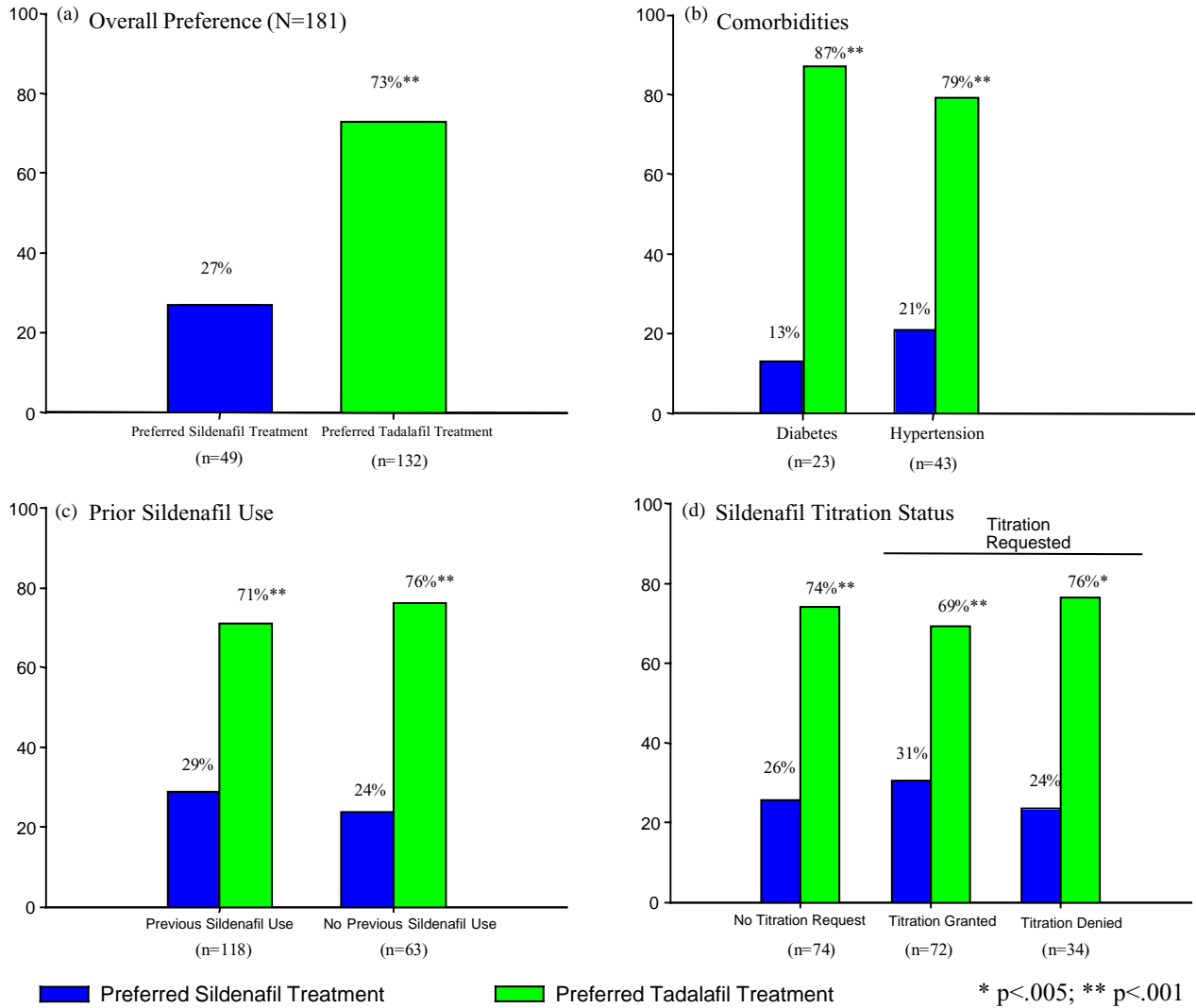


Fig. 4. Patient preference for sildenafil vs. tadalafil overall and by comorbidities, prior sildenafil use, and sildenafil titration status.

with active medication. Physicians and patients were blinded to the status of their request. Most patients who made a titration request (91%) chose a treatment for the Extension Period. Of these patients, 72 had titrated to sildenafil 100 mg and 34 had remained at 50 mg.

The baseline patient characteristics of these two respective groups of patients were similar (data not shown). Most patients who titrated to sildenafil 100 mg preferred tadalafil (69%, $p < 0.001$). Similar results were noted among patients who remained on sildenafil 50 mg (76%, $p = 0.002$). Of the patients who did not make a titration request, 74% preferred tadalafil ($p < 0.001$, Fig. 4d).

3.3. Dosing instruction preference

Of the 36 patients in the Dosing Instruction Preference Assessment who chose a treatment for the Extension

Period, 24 (67%) preferred tadalafil with tadalafil dosing instructions and 12 (33%) preferred tadalafil with sildenafil dosing instructions ($p = 0.046$).

3.4. Dosing and sexual attempt timing

Patients in the Drug Preference Assessment recorded 5834 sexual attempts during tadalafil treatment and 5461 sexual attempts during sildenafil treatment. The mean time between dosing and sexual attempt was 5.6 ± 3.9 (mean \pm S.D.) hours for tadalafil and 2.7 ± 2.6 hours for sildenafil ($p < 0.001$). Approximately half of the patients taking tadalafil (55%) and 29% of patients taking sildenafil recorded at least one initial sexual intercourse attempt 12 or more hours after dosing ($p < 0.001$). Additionally, 13% and 3% of all initial sexual intercourse attempts following dose of study drug occurred 12 or more hours after taking tadalafil and sildenafil, respectively.

Table 2

Incidence of treatment-emergent adverse events among patients in the Drug Preference Assessment (Treatments Arms 1 and 2; $n = 219$)^a

Event	Tadalafil n (%)	Sildenafil n (%)
Headache	26 (11.9)	17 (7.8)
Dyspepsia	14 (6.4)	10 (4.6)
Back pain	9 (4.1)	4 (1.8)
Myalgia	9 (4.1)	1 (0.5)
Flushing	6 (2.7)	8 (3.7)
Nasal congestion	6 (2.7)	10 (4.6)
Influenza-like illness	3 (1.4)	7 (3.2)

^a Data are given as number (%); events listed occurred in $\geq 2\%$ of patients with either treatment.

3.5. Safety

Sildenafil and tadalafil were well tolerated. In the Drug Preference Assessment, four patients discontinued the study because of adverse events during tadalafil treatment. One patient each reported abdominal pain, acute myocardial infarction, congestive heart failure, or headache. Three patients discontinued during sildenafil treatment because of adverse events. One patient each reported coronary artery disease, dyspnea, or acute myocardial infarction. In the Dosing Instruction Preference Assessment, no patients discontinued the study because of adverse events.

Treatment-emergent adverse events experienced by 2% or more of patients in the Drug Preference Assessment are summarized in Table 2. Treatment-emergent events that occurred in more than one patient in the Dosing Instruction Preference Assessment were dyspepsia (5 patients, 10.9%), headache (2 patients, 4.3%), influenza-like illness (2 patients, 4.3%), and nasopharyngitis (2 patients, 4.3%).

4. Discussion

In the Drug Preference Assessment of this randomized, double-blind, crossover study, 73% of men with ED preferred tadalafil compared to 27% who preferred sildenafil ($p < 0.001$). Similar percentages of tadalafil preference were observed in most of the patient subgroups evaluated. Of particular note, 71% of patients who used sildenafil prior to the start of the study and 76% of sildenafil naïve patients preferred tadalafil ($p < 0.001$). In the Dosing Instruction Preference Assessment in which patients took tadalafil with sildenafil or tadalafil dosing instructions, a majority (67%) of patients preferred the tadalafil dosing instructions ($p = 0.046$). Additionally, patients appeared to engage in sex over a broad time frame after taking tadalafil. For sildenafil, the mean time interval between

dosing and sexual attempt was within the dosing instructions' recommended time frame. However, some sexual attempts occurred 12 or more hours after taking sildenafil.

Both sildenafil and tadalafil were well tolerated. In all the treatment arms, only seven patients discontinued the study because of adverse events, four during tadalafil treatment and three during sildenafil treatment. The incidence of treatment-emergent adverse events for the entire study was low and comparable to the rates found in other PDE inhibitor studies [12,20–22].

Among patients in the Drug Preference Assessment, 58% and 48% of patients in Treatment Arms 1 and 2, respectively, requested titration with physician approval ($p = 0.026$). Those patients for whom titration requests were granted with active medication took sildenafil 100 mg for the final eight weeks of the treatment period, a sufficient amount of time to adjust to the higher dose. The majority of patients (69%) who received sildenafil 100 mg nevertheless still preferred tadalafil ($p < 0.001$), as did the majority (76%) of those whose titration request, unbeknownst to them, was not granted ($p = 0.002$).

One obvious limitation of this study pertains to the 35% limit on titration to sildenafil 100 mg. Definitive data on the relative use of sildenafil in clinical practice are difficult to obtain because of the possibility of pill splitting with the sildenafil 100 mg tablet. Thus, although this limit on the proportion of patients who could increase their dose to 100 mg has support in the literature [17–19], the limit may not accurately reflect the proportion of patients for whom the sildenafil dose is limited to 50 mg in clinical practice. Additionally, as a result of the titration limit, some patients who requested titration did not receive their desired treatment. This included 26% and 15% of patients taking sildenafil in Treatment Arms 1 and 2, respectively, and all patients taking tadalafil in Treatment Arms 3 and 4. Patients and their physicians were blinded as to whether their titration request had been granted to ensure that they could not identify the study drug. Physicians and patients were, however, aware of this study methodology. The protocol described the 35% limit on titration. The informed consent document also instructed patients that they may have an opportunity to increase their dose, but that they would not know the dose they were taking.

Despite this limitation, the conclusion regarding the overall preference for tadalafil is supported by the finding that tadalafil was significantly preferred over sildenafil within each of the following three subgroups of patients: (1) those who did not request titration, (2) those who requested titration and whose

request was granted, and (3) those who requested titration but whose request was not granted because the limit was reached. The overall preference result is further supported by the finding that the latter two subgroups were comparable in terms of baseline demographics.

A second limitation was that 20 mg was the only tadalafil dose used in this study. When the study was designed tadalafil 20 mg was proposed as the recommended starting dose for ED treatment. The approved recommended starting dose in some countries is 20 mg, while in other countries the recommended dose is 10 mg. Had the 10 mg tadalafil dose been used in this study, the preference results might have been different.

A third limitation was that downward titration to either sildenafil 25 mg or a return to sildenafil 50 mg was not permitted in the protocol. However, the inability to titrate downward to 25 mg is unlikely to have significantly impacted the results, because past sildenafil flexible-dosing studies show most patients increasing to and/or maintaining doses of 50 mg and 100 mg [9,23–26]. Also, common treatment-emergent adverse events for sildenafil, such as dyspepsia, are often indicative of the need for downward titration. However, low rates of discontinuation due to these adverse events were observed in this study.

All previous sildenafil users were enrolled in the study irrespective of their response to the drug. However, data discriminating between sildenafil responders and non-responders were not recorded. Therefore, the question of patient preference for tadalafil among sildenafil non-responders is not extractable from our data.

Another limitation was that while the study was double-blind, both investigators and patients knew that sildenafil with tadalafil dosing instructions was not one of the possible combinations used in this study. Patients treated with sildenafil were given only sildenafil dosing instructions to comply with the sildenafil package insert and to protect against an efficacy bias against sildenafil by encouraging its use outside its temporal window of maximal efficacy.

The tadalafil dosing instructions were also a potential source of bias. The tadalafil dosing instructions highlighted the flexibility of the study drug by providing possible time intervals between dosing and sexual attempt. The dosing instructions also suggested that the patient may experience improved flexibility and spontaneity in his sexual relationship. In contrast, the dosing instructions for sildenafil were those provided by the manufacturer and no additional information was provided. This elaboration of the tadalafil dosing

instructions may have influenced the behavior and responses of the patients.

Despite all these limitations, this is one of the first studies to assess preference between oral treatments for ED and to employ a methodology to enhance blinding for ED medications with different dosing instructions. A final limitation, however, is this study did not thoroughly assess the reasons for patient preference. The tadalafil dosing instructions were clearly preferred when drug treatment was held constant (tadalafil) and the increased window of opportunity afforded by these dosing instructions might well have contributed to the specific drug preference. Future studies are needed to determine the reasons for the preference for tadalafil over sildenafil and the attributes of ED treatments in general that influence patient preference.

5. Conclusion

In conclusion, 73% of patients in the Drug Preference Assessment preferred tadalafil over sildenafil. Sildenafil and tadalafil were administered with their respective dosing instructions. In addition, 67% of patients in the Dosing Instruction Preference Assessment preferred tadalafil administered with tadalafil dosing instructions over sildenafil dosing instructions. The results of our study are subject to several potential limitations including the 35% limit imposed on titration to 100 mg sildenafil and more detailed patient instructions for tadalafil. Despite these limitations, this is one of the first studies to assess preference between PDE-5 inhibitor drugs for ED and the only study to date to employ a methodology to help ensure blinding for ED medications with different dosing instructions.

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Editorial Comment

I. Eardley, *Leeds, United Kingdom*

At a time when there are three PDE5 inhibitors licensed for the treatment of erectile dysfunction in many parts of the world, one of the issues which face both physicians and patients is which drug to use? The answer to such questions may be determined by differences in efficacy, differences in safety and side effect profile or by issues relating to onset and duration of action. Such issues can be addressed in comparative trials, either using a crossover or a parallel group design. A further way of comparing drugs is to use a “preference” study, such as is reported here. Patient preference for a drug will be influenced by many of the drug related issues outlined above and by other issues relating to the population that is included in the study. The ideal preference study might be expected to predict

the behaviour of a population, although its ability to predict the behaviour of an individual is somewhat limited.

For a preference study to give a meaningful answer, then it should be fair to both drugs. One possible design would be a fully blinded randomised crossover study with assessment at the end of treatment period and with an adequate washout period. Although the study reported above has some of these features there are a number of defects in study design which are likely to have resulted in a biased and inaccurate result. Firstly, the comparison of tadalafil 20 mg and variable dose sildenafil is inappropriate, even though 20 mg tadalafil is the only drug licensed in some parts of the world. Second, the 35% limit on those patients who were able to titrate up to the top dose of sildenafil is unduly restricting and unfair. Third the information sheets as presented do demonstrate bias in the extent of the

explanation and information given to the patient, again in favour of tadalafil. Finally, in such a study, the use of treatment naïve patients would be preferable, so that the effects of prior experience can be excluded.

This study showed that 73% of men preferred tadalafil to sildenafil. However, the defects in study design limit its applicability to the general population and further studies with better designs need to be performed before any firm conclusions can be drawn.

Editorial Comment

F. Montorsi, *Milan, Italy*

This is a double-blind study assessing patient preference between tadalafil and sildenafil in patients with erectile dysfunction of diverse aetiology. The results suggest that the majority of the patients favored tadalafil over sildenafil and the tadalafil dosing instructions over the sildenafil dosing instructions.

The take home message of the paper would thus seem straightforward: however, I strongly believe we should be very cautious in drawing final conclusions from this paper. Hereafter are my major concerns.

1. Tadalafil has been approved for marketing in the EU and US having the 10 mg dose as the recommended starting dose. Thus, it would seem logical to run a flexible dose study having 10 mg and 50 mg as starting doses for tadalafil and sildenafil, respectively. The authors recognize in the discussion section of the paper that this is a major limitation for this study.
2. Only 35% of patients receiving 50 mg of sildenafil were given the possibility to receive 100 mg of the drug if needed. The authors state in the paper that this reflects every day experience. However, if this concept was really acceptable, it would be also true that probably not all patients would request 20 mg tadalafil. The comparison seems to be not fair to me.
3. I agree with the authors' introductory comment on the need of new drugs for erectile dysfunction as a significant number of patients being treated with sildenafil ultimately decide to stop using the drug for a number of diverse reasons. At present we are lacking the knowledge of a precise reason for this. However, it is possible that this will happen also with other PDE5 inhibitors. I would like the readers of *European Urology* to be aware of this.
4. Absence of food interaction with tadalafil. A well designed study has shown that the T_{\max} and C_{\max} of tadalafil do not change after a meal as compared to the fasting state. This is certainly a factor of major importance for any drug. I would like to emphasize here however that in my every day practice I have the feeling that tadalafil is best spent if used at a distance from sexual activity: in this setting, food interaction loses some of its importance. What I have been telling my patients is to take tadalafil early in the morning if they are used to have sex in the afternoon, take tadalafil at 11.00 a.m. if they are used to have sex in the evening and take the drug at bedtime if they like to have sex early in the morning. I usually see that the concept of taking the drug and subsequently forgetting about it is well accepted by patients. By following this strategy, the interaction with food is always avoided. Please do remember that the impact of food seemed to be minor also with sildenafil but the postmarketing experience showed it was not the case. I have also been using sildenafil and vardenafil in a slightly different way than the usual one: in patients who favor sexual activity as an after dinner entertainment, I suggest them to take the drug an hour prior to dinner. This would allow the drug to be absorbed by the time they start their meal. Usually these patients are covered for the following 4 to 6 hours and they can happily engage in sexual intercourse with both sildenafil and vardenafil. These are personal experiences with patients that clearly need to be confirmed by properly designed studies and I would recommend readers of *European Urology* to build up their own clinical experience on this regard.
5. Are tadalafil dosing instructions better than sildenafil dosing instructions? It is clear to everybody that if a pill can be used successfully from 30 minutes to 36 hours after ingestion as compared to another one which can be used from 1 to 4 hours after administration, most of the patients would probably opt for the first one. I have two remarks here: we do not know whether tadalafil and sildenafil are actually providing patients with similar erectile responses an hour or so after administration. My personal experience suggests to me that sildenafil is more efficacious than tadalafil in the same patient when sexual intercourse is engaged 30 to 60 minutes after the administration of the drug. On the contrary, tadalafil is allowing most of the patients to have sex at a long distance from ingestion of the pill and this effect is clearly much less evident with sildenafil, although there may be exceptions. I have the feeling that there may be patients who want something which works real fast while others would be more pleased by the extended period of responsiveness: thus patients will choose one or the other drug according to their

specific needs. With regards to the present manuscript, it is clear to me that using sildenafil dosing instructions with tadalafil is the worse way to use a wonderfully effective drug as tadalafil.

Lastly, I would respectfully suggest pharma companies sponsoring prospective trials to limit the number of their employees in the authors' list. This is reducing the scientific strength of the manuscript.