Prospective, Randomized, Open-Label, Fixed-Dose, Crossover Study to Establish Preference of Patients with Erectile Dysfunction after Taking the Three PDE-5 Inhibitors

Josep Rodríguez Tolrà, MD, José María Cuadrado Campaña, MD, Lluis Fumadó Ciutat, MD, and Eladio Franco Miranda, MD

Hospital Universitario de Bellvitge—Urology, L'Hospitalet, Barcelona, Spain

DOI: 10.1111/j.1743-6109.2006.00297.x

ABSTRACT

Introduction. We conducted a prospective, randomized, open-label, fixed-dose preference study, with a crossover design, using sildenafil, vardenafil, and tadalafil.

Aim. To assess patient preference for sildenafil (100 mg), vardenafil (20 mg), and tadalafil (20 mg) for the treatment of erectile dysfunction. Secondary objectives included finding out whether patients would follow treatment with a second or third option, in the event that the preferred drug was not available, and to assess side effects.

Main Outcome Measures. Patient preference for any treatment, and evaluation of the elements that patients would assess when choosing one of these drugs.

Material and Methods. Sildenafil (100 mg), vardenafil (20 mg), and tadalafil (20 mg) were taken at least six times over a period of 45–60 days with a washout period of 7 days. A total of 132 patients were enrolled to achieve a valid sample of 90 cases (15 per randomized group, total of six groups). Enrolled patients had mild to moderate erectile function.

Results. The International Index of Erectile Function (IIEF) score improved from baseline and was statistically significant in all cases ($P < 0.0001$). When we compared the IIEF scores, we found a statistically significant difference between tadalafil and vardenafil ($P = 0.0002$) favoring the former; similar results were obtained with the Erectile Dysfunction Inventory for Treatment Satisfaction (EDITS) Questionnaire ($P = 0.000075$). We also found a significant difference ($P = 0.012$) between tadalafil and sildenafil, again in favor of the former. In assessing drug preference, 25 patients (27.77%) chose sildenafil, 18 (20%) vardenafil, and 47 (52.22%) tadalafil. A total of 94% of patients would be willing to take another drug if the preferred choice was not available. All drugs were well tolerated.

Conclusions. Although this is a preference study based on subjective elements, statistically significant differences comparing the IIEF score and the EDITS Questionnaire lead us to believe that beyond patients' subjective preference *per se*, said preference is probably also based on a genuinely superior response to one drug over another.

Tolrà JR, Campaña JMC, Ciutat LF, and Miranda EF. Prospective, randomized, open-label, fixed-dose, crossover study to establish preference of patients with erectile dysfunction after taking the three PDE-5 inhibitors. J Sex Med 2006;3:901–909.

Key Words. Erectile Dysfunction; Sildenafil; Vardenafil; Tadalafil; Phosphodiesterase-5 Inhibitors; Patient Preference; Randomized Study

Introduction

Erectile dysfunction affects some 152 million men worldwide [1]. It is a disorder that impairs their self-esteem, marital relations, and compromises the quality of life of both patients and their partners [2–6].

Joint decision making between patients and physicians is becoming more and more common; hence, the assessment of patient preference is of growing relevance [7].

Studies addressing preference between oral drugs (sildenafil) and other treatment modalities have been carried out [8,9], and studies that deal

with preference between two phosphodiesterase (PDE)-5 inhibitors (sildenafil and tadalafil) have begun to appear [10–12]. But there are few reports comparing these three PDE-5 inhibitors.

Numerous studies back up the efficacy and tolerance of the three PDE-5 inhibitors in the treatment of erectile dysfunction [13–20]; but, these are only two of the factors that are involved in a person's decision to continue using a given treatment. There are other issues, such as the couple's relationship, privacy, and quality of life [21–24], that can tip the balance to one side or the other when deciding.

Moreover, in the treatment of disorders for which there may be more than one drug of the same treatment group (as is the case with PDE-5 inhibitors), patient preference can be a very important criterion that physicians should take into account, particularly in the case of erectile dysfunction, in which response depends heavily on subjective factors.

Consequently, the main objective of the present independent and unsponsorized study was to evaluate efficacy and patient preference throughout treatment periods of 6–8 weeks with sildenafil 100 mg, vardenafil 20 mg, and tadalafil 20 mg, taken as per their respective instructions for administration. Secondary objectives consisted of determining patient tolerance to the drugs and finding out whether the patients would continue treatment with another drug other than the one they had chosen, in the event that it was unavailable.

Materials and Methods

Study Design

We used a prospective, open-label, randomized, fixed-dose trial with a crossover design in order to establish the degree of preference in patients with erectile dysfunction after taking the three PDE-5 inhibitors, administered sequentially, and using the patients as their own controls.

The doses at start-up were the following: 100 mg of sildenafil and vardenafil, and 20 mg of tadalafil. Patients had to try each drug a minimum of six times, and medication was not provided by investigators, reflecting usual standard of care.

The instructions given to patients were the specific instructions of use for each treatment each time the medication was prescribed.

Each drug had to be taken a minimum of six times over a period of 45–60 days; furthermore, a drug washout time was established, during which participants would remain without treatment for 1 week in order to avoid the residual effect when switching medication. This study was conducted June 2003 through September 2005.

Patients

Patients were enrolled in the study if they met all inclusion and none of the exclusion criteria, based on the following: men aged 18 years or older, with heterosexual relations, erectile dysfunction of more than 6-month evolution, and presenting figures indicative of moderate to mild dysfunction according to the International Index of Erectile Function (IIEF) administered at the evaluation visit.

All patients were naïve to treatments and had not previously taken any PDE-5 inhibitor. Patients undergoing treatment with nitrites, who had a recent history of myocardial infarction (less than 6 months previous) or unstable angina were not candidates for enrollment in the study. Patients with resting hypertension of systolic pressure (SP) > 170 or diastolic pressure (DP) > 110, or resting hypotension of SP < 90 were also excluded from participation in the study, as were men with retinitis pigmentosa or a history of hepatitis B or C. Finally, patients taking androgens, cytochrome P-450-3 A4 inhibitors, or alpha blockers also were excluded.

Patients gave verbal informed consent before participating in the study. Because this is an open-label study with three commercialized drugs, written informed consent was considered unnecessary. Patients received usual standard of care drug instructions and were asked whether they would like to participate in this trial to evaluate the three drugs.

Randomization and Sample Size

The same number of patients was randomized to each treatment arm until the entire sample was completed.

Six treatment groups were set up with the following sequences:

Group 1: sildenafil 100, vardenafil 20, and tadalafil 20 mg;
Group 2: sildenafil 100, tadalafil 20, and vardenafil 20 mg;
Group 3: vardenafil 20, sildenafil 100, and tadalafil 20 mg;
Group 4: vardenafil 20, tadalafil 20, and sildenafil 100 mg;

Group 5: tadalafil 20, sildenafil 100, and vardenafil 20 mg;
Group 6: tadalafil 20, vardenafil 20, and sildenafil 100 mg.

In order to achieve a valid sample of 90 subjects (15 per group and factoring in dropouts and protocol violations), 132 men were thought to be needed (22 per group).

Objectives

There were two main objectives in this study. First, we wanted to evaluate the efficacy of these drugs. Therefore, all the participants were required to fill in the IIEF [25] at the admission visit and then again, after taking each of the drugs. Likewise, after taking each drug, the subjects filled in the Erectile Dysfunction Inventory for Treatment Satisfaction (EDITS) Questionnaire [23], which measures the degree of satisfaction with the treatment received.

The second main objective consisted of evaluating subjective elements that the patients would be taking into account when choosing one of the three PDE-5 inhibitors.

The secondary objectives involved finding out whether, in the case that the product ranked first did not exist, the patients would continue treatment with one of the other drugs that they had not chosen. The adverse effects of each drug were also assessed, and we compared them to see in which cases side effects were significant enough for the patient to give up the medication or to condition taking it in the future.

Outcome Analysis

(a) We compared the results of the IIEF at the in-take visit with the figures obtained after taking each drug.
(b) We compared the results of the IIEF after taking each drug with the results obtained after taking the other medications.
(c) We compared the score on the EDITS Questionnaire after taking each drug with the results obtained after taking the other medications. The EDITS Questionnaire is an 11-item questionnaire with five possible answers for each question. (Each answer is assigned a value of 0–4, providing final scores that range from 0 to 44.)
(d) We analyzed the patient's drug selection criteria.
(e) We also examined whether the participant would continue treatment with either of the other two products if the medication to chose was not available.
(f) The secondary effects associated with each drug were quantified, and subjects were asked whether these effects would force them to stop taking the medication or whether the effects would condition their taking it again in the future.

Statistical Analysis

A 90-patient sample size was deemed sufficient to determine preference for sildenafil, vardenafil, or tadalafil. The sample size was calculated for an alpha risk of 0.05 and statistical power of 80%, bearing in mind a minimum intergroup difference of two points in perception on the EDITS test.

A one-factor ANOVA was used to test the null hypothesis that there were no differences between treatments. A level of significance of $P < 0.05$ was needed to prove the null hypothesis.

The descriptive analyses of the quantitative variables were carried out using the means, medians, and percentiles 10–90.

The qualitative variables are expressed as percentages, and the comparison of means was performed by means of the one-factor analysis of variance; subsequently, a Bonferroni post-hoc test was conducted.

The statistical software used was SPSS, version 11.5.

Results

In order to complete a valid sample of 90 patients (15 per group), 132 subjects had to be enrolled. Twenty-five patients were lost to follow-up, 11 did not comply with the protocol, and six were not included due to the fact that a sample size of 90 patients was considered sufficient.

The mean patient age was 53.79 years (range 27–67 years), and there were no significant differences between groups of treatment order ($P = 0.751$). All patients were Caucasian and a minority were of Latin American origin. The etiology of erectile dysfunction was organic and mixed in some patients, with diabetes, hypertension, dislipidemia, and cardiovascular conditions being the most common comorbidities associated. In most cases, more than one condition was associated.

The median for the IIEF at the in-take visit was 17 (percentile 10–90: 11–23), and there were no significant differences between groups of treatment order ($P = 0.277$).

Table 1 Pre- and post-treatment median and percentile values of IIEF

	Median	Percentile 10–90
IIEF pretreatment	17	11–23
IIEF post-sildenafil	29	25–30
IIEF post-vardenafil	28	23.10–30
IIEF post-tadalafil	30	25–30

IIEF = International Index of Erectile Function.

Table 2 Post-treatment median and percentile values of EDITS

	Median	Percentile 10–90
EDITS post-sildenafil	38	34–43
EDITS post-vardenafil	37.5	29–42
EDITS post-tadalafil	41	33–44

EDITS = Erectile Dysfunction Inventory for Treatment Satisfaction.

In short, there was good intergroup heterogeneity. After taking sildenafil, the median for the IIEF was 29 (percentile 10–90: 25–30), after taking vardenafil, it was 28 (percentile 10–90: 23.10–30), and after taking tadalafil, it was 30 (percentile 10–90: 25–30) (Table 1). In all three of these cases, the treatments were efficacious in terms of the change in the IIEF score vs. baseline ($P < 0.0001$).

Using the IIEF assessment tool to compare the three drugs posttreatment, we found statistically significant differences ($P < 0.0001$). These differences are detected between tadalafil and vardenafil (in favor of the former) with a P value of 0.00022. We found no differences between tadalafil and sildenafil ($P = 0.095$), or between sildenafil and vardenafil ($P = 0.085$). In short, tadalafil is superior to the other two, although it only achieves a level of statistical significance with respect to vardenafil (Figure 1).

The application of the EDITS Questionnaire after taking each drug gave the following results: after taking sildenafil, the median was 38 (percentile 10–90: 34–43), post-vardenafil, it was 37.5 (percentile 10–90: 29–42), and post-tadalafil, it was 41 (percentile 10–90: 33–44) (Table 2). These differences were statistically significant ($P < 0.0001$). In this case, tadalafil was proven to be superior to the other two drugs ($P = 0.000075$ for vardenafil and 0.012 for sildenafil); we found no differences between sildenafil and vardenafil ($P = 0.273$). In brief, as quantified by the EDITS assessment tool, tadalafil rates were better than sildenafil and vardenafil, whereas no differences were detected between sildenafil and vardenafil (Figure 2).

Of the 90 patients who completed the study, 25 (27.77%) opted to continue with sildenafil, 18 (20%) chose vardenafil, and finally, 47 (52.22%) preferred to continue with tadalafil (Figure 3).

When the criteria that motivated the participants to continue using one drug over the others were subject to analysis, we found the following:

(a) Of the 25 patients who chose sildenafil, 21 did so because they reported that the drug enabled them to achieve a more intense and longer-

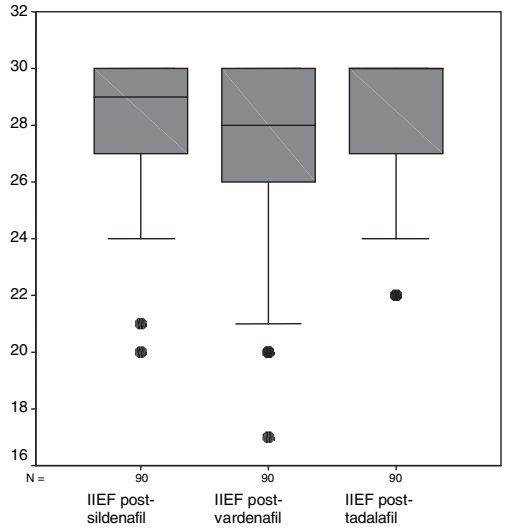

Figure 1 IIEF data presented with median and percentile 10–90.

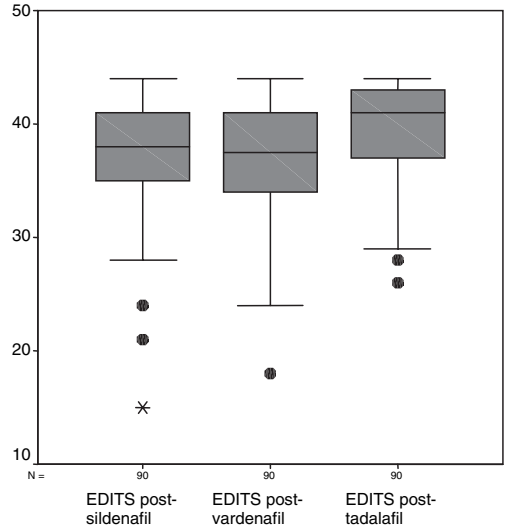

Figure 2 EDITS data presented with median and percentile 10–90.

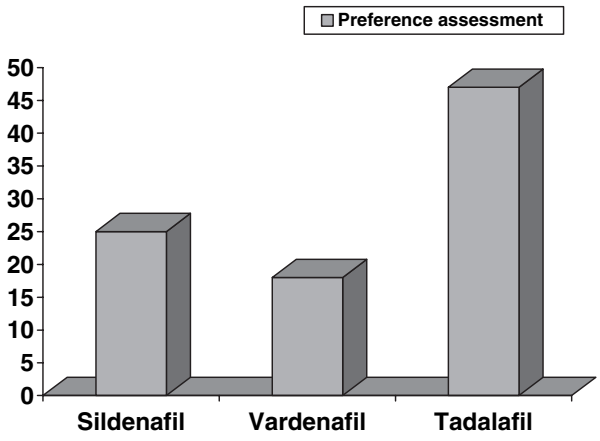

Figure 3 Preference assessment after treatment.

lasting erection; one chose it because erection occurred more quickly; and three of those who would have chosen tadalafil because they felt that the erection they achieved was better quality, finally opted in favor of sildenafil because tadalafil provoked myalgia in two cases, and in one case, it produced headaches that were intense enough for the participant to want to discontinue with the medication.

(b) Of the 18 patients who chose vardenafil, 16 chose it because it provided them with a more intense and longer-lasting erection, one because erection occurred more quickly, and one because it had fewer side effects than the other two drugs.

(c) Finally, we can see how the criteria for choosing tadalafil were more varied. Of the 47 patients who chose it, 11 did so because they stated that it was the one that enabled them to achieve a more intense and longer-lasting erection, without commenting on the possibility of having intercourse a second time the next day. Three patients chose it because of the flexibility it provided them by being able to take it at any time of the day. For five participants, the feeling that they could have intercourse again the following day, even if they ended up not doing so, was what tipped the balance in favor of tadalafil. Three people who would have preferred sildenafil and another one who would have chosen vardenafil finally opted in favor of tadalafil on the basis of secondary effects. Twenty-three patients (25.55%) stated that with the same-quality erection during the first intercourse, the fact that they could have intercourse again the next day was the reason for their decision.

It is also important to point out that when asked whether patients would choose to continue treatment with one of the other two alternatives if their drug of choice was not available, the response was affirmative in 93.71% of the cases.

Adverse events are presented in Table 3.

Seven subjects stated that they would not continue with sildenafil: five because of side effects, and in two cases because it failed to meet their expectations. Six patients would not continue with vardenafil: two in light of secondary effects, and four because it failed to meet their expectations. Five patients said that they would not continue with tadalafil because of the secondary effects. It is important to underscore the fact that these adverse effects only required the subject to stop taking the medication in five cases with sildenafil, five with tadalafil, and two with vardenafil. If we take into account the fact that 270 treatments took place with the 90-patient sample, only 12 patients (4.44%) dropped out.

Discussion

All the PDE-5 inhibitors have been proven to be highly effective. The good response to these drugs is independent of age and race, as well as etiology and time of evolution. The best results are obviously going to be seen in patients with mild to moderate erectile dysfunction. To assess patient preference in this study, patients responding to therapy were considered the best choice. For that reason, only patients with mild to moderate erectile dysfunction were included and maximum doses of each drug given.

Numerous studies endorse efficacy vs. placebo in the case of sildenafil [19,26–28]. Vardenafil would possibly stand apart given its pharmacokinetics, in that it would reach a maximum serum concentration within a shorter period of time. Several studies also prove its efficacy [18,29–31]. The most outstanding differential characteristic of tadalafil compared with the others is its longer

Table 3 Adverse events after treatment

	Sildenafil (%)	Vardenafil (%)	Tadalafil (%)
Headache	11.11	12.22	8.88
Flushing	7.77	3.33	4.44
Dyspepsia	4.44	5.55	3.33
Myalgia	—	—	4.44
Nasal congestion	1.11	1.11	2.22
Tachycardia	4.44	1.11	1.11
Vision disorders	4.44	3.33	3.33

half-life. In this case, its overall efficacy has also been amply demonstrated [13,14,32,33].

Associated adverse effects may affect 10–40% of the patients treated; nonetheless, it is also true that dropouts due to these adverse effects do not generally exceed 2–6%; in the participants in our study, only 5.18% discontinued treatment.

We have proven that efficacy and tolerance would be the two most important considerations when choosing a drug treatment. However, when different medications provide similar benefits, insofar as efficacy and tolerability are concerned, other characteristics can determine preference in choosing the drug.

The first preference studies compared sildenafil and a vacuum erection device [8] or with intracavernous prostaglandin injection therapy [9,34,35]. Nevertheless, there are very few studies that have investigated preference among PDE-5 inhibitors, and when this issue has been the object of evaluation, the majority of these studies have only compared two drugs.

The first preference study comparing sildenafil and tadalafil that we have found was the one conducted by Ströberg et al. [11]. In their study, 90% of the patients chose tadalafil; however, in our opinion, the study design may have skewed the results in favor or tadalafil, because, first of all, only 35% took a 100-mg dose of sildenafil vs. a 20-mg dose of tadalafil in all cases; the remaining participants took lower doses of sildenafil. Second, all the patients had previously taken sildenafil and were switched over to tadalafil for 9 weeks and then were asked to decide which drug they would prefer to take. These two facts can condition the final outcomes.

We believe that the results that appear in Govier et al.'s study [10] (66.3% preference in favor of tadalafil vs. 33.7% in favor of sildenafil), better reflect reality, as it was a randomized, double-blind, crossover, fixed-dose study. The only shortcoming we would point out in this study is its short duration and the fact that a 50-mg dose of sildenafil vs. a 20-mg dose of tadalafil was used in all cases; this is relevant because had the study called for 100 mg of sildenafil, the results might have been different.

Von Ketz et al.'s work [12], the main part of which has a design that is very similar to Govier et al.'s study [10], is different in that when a 50-mg dose of sildenafil is used, there is the possibility of an upward dose titration. The result of 73% in favor of tadalafil vs. 27% who preferred sildenafil might also have been different had the possibility of the upward dose titration for tadalafil not been included in the design.

We have also found preference studies in the form of short reports or posters in which sildenafil has also been compared with tadalafil, albeit the outcomes are difficult to evaluate given that in some cases, the sildenafil doses used are not specified [36–38] and in others, all the patients had come off treatment with sildenafil [36,38,39].

The articles we found that deal with preference and compare all three of these PDE-5 inhibitors are also in the form of posters or short reports. Of them, the one by Claes and Van Poppel [40] that reports preference data of 32% (tadalafil), 32% (sildenafil), and 36% (vardenafil), does not specify the dosages administered of each drug, nor does it refer to sequences or the presence or absence of washout periods. Moreover, in their results, tadalafil is the drug of choice when dysfunction is mild, going down to the last place when the dysfunction is severe. The opposite occurs in the case of vardenafil, which we find illogical, and we do not believe their results to be of much value. The work conducted by Park et al. [41] in 67 patients establishes preferences of 19.4% (tadalafil), 55.2% (sildenafil), and 25.4% (vardenafil); however, it mixes patients for whom doses were 10–50–10 mg with others who received doses of 20–100–20 mg and without specifying the number of patients included in each group. It also fails to specify the sequence in which the drugs were administered or whether or not there was a washout period; hence, we consider that these results also are not very valid. The work by Prost et al. [42] was carried out with 222 patients and offers preference figures of 44% tadalafil, 32% vardenafil, 14% sildenafil, and 10% who expressed no preference. It does not specify doses, sequence of administration, number of times each drug is taken, or whether or not there was a washout period. In light of these limitations, we would also question the value of these results. Another work by Prost [43] was performed with a group of 107 diabetic patients and provides the following results: 36% (tadalafil), 15% (sildenafil), 28% (vardenafil), and 21% (no preference). These outcomes would be of greater value were it not for the fact that this study also mixes patients in whom dosages of 10–50–10 mg were used with others who took doses of 20–100–20 mg; furthermore, 68% of the patients had come off taking sildenafil for more than 25 months. It also fails to mention the presence or absence of a washout period. We have found two publications by Sommer et al. [44,45] with the

same design. We will comment on the second one because it used the same doses as the ones used in our study (100–20–20 mg). Eighty-six patients completed the prospective, randomized, open-label, placebo-controlled, crossover study that included a washout period. The results that the authors present, particularly as regards the efficacy of the drugs vs. placebo, are very valid; however, the part that refers to patient preference (tadalafil, 40%; sildenafil, 18%; vardenafil, 43%) is not so valid because the use of placebo makes it impossible to give the instructions of use for each drug. These differences in use might have a bearing when choosing a drug.

Finally, we will cite the work carried out by Stroberg et al. [46] as 145 patients completed the trial at maximum doses, and the preference data are as follows: 53% were in favor of tadalafil, 25% preferred sildenafil, 15% chose vardenafil, and 5% did not respond. These results are similar to ours: 52.22% tadalafil, 27.77% sildenafil, and 20% vardenafil. Nonetheless, this work also presents certain objectionable aspects such as: 66% of the patients had been previously treated, there was no drug washout, and the sequence consisting of four tablets of 100-mg sildenafil, four tablets of 20-mg vardenafil, and finally, eight tablets of 20-mg tadalafil may skew the results in favor of tadalafil.

In summary, 52.22% of the participants in our study opted in favor of tadalafil compared with 27.77% who preferred sildenafil, and 20% who chose vardenafil as their number-one choice; all these drugs were used at all times in accordance with their respective instructions for administration.

We do not know the clinical relevance of the statistical differences shown in the results of the present study. We believe that the design used is good enough for the results to be taken into account, as it is one of the few studies in which PDE-5 inhibitor preference has been assessed in treatment responders. Potential limitations of this study are that it was conducted in only one center and due to lack of sponsorship, only 90 patients were included. A larger sample size would have given greater accuracy to the results, even if the actual sample size was sufficient for statistical significance. The open-label design may have had some impact upon patient response to treatments, but no bias favoring any of the three drugs should be expected from the design of the study. Patients were given the three drugs in all sequences to avoid period, sequence, and recall effects. Patients know what treatment they are on, its attributes, and limitations, and thus asses whether these factors are important enough to tilt the balance in favor of any of these drugs.

Furthermore, we must point out that although it is a preference study, validated instruments such as the IIEF [25] and the EDITS Questionnaire [26] (male version) have also been used and administered after taking each drug. It is also worth indicating that statistically significant differences emerge with respect to tadalafil and vardenafil according to the rating on both tests; the same can be said between tadalafil and sildenafil when the EDITS Questionnaire is used, whereas neither of the two tests demonstrates significant differences between sildenafil and vardenafil. All of this shows us that beyond patients' subjective preference, said preference would be based on the superior effectiveness of one drug over another. It is likely that with more cases, these results might be even more conclusive.

Conclusions

The first conclusion is that all three of these PDE-5 inhibitors produce an important improvement in erectile function, which is revealed by comparing the IIEF score before and after taking each drug. However, it is also important to note that this improvement is not identical in all the cases. When we compare the results of the IIEF and EDITS Questionnaire (patient version) after taking each drug, we find that there are statistically significant differences between tadalafil and the other two drugs—differences that are not significant between sildenafil and vardenafil.

Insofar as patient preference is concerned, the main criterion when choosing drugs is that the first erection should be as intense and long-lasting as possible. Although it is also true that given the same quality of the erection attained, patients choose tadalafil because it is easier to take and they can take it at any time of the day and, above all, because of the feeling or the actual possibility of having intercourse again the next day.

We would also like to highlight the fact that when asked whether they would continue treatment with one of the other drugs if their drug of choice was not available, 93.71% of the participants said yes.

Finally, we would like to point out how few side effects conditioned drug choice and the fact that secondary effects rarely led the person to discontinue treatment (only 12 treatments out of 270).

Corresponding Author: Josep Rodríguez Tolrà, MD, Hospital Universitario de Bellvitge – Urology, feixa llarga s/n, L'Hospitalet, Barcelona, 08907, Spain. Tel: 00 34933840803; Fax: 00 34932607624; E-mail: jrtol@wanadoo.es

Conflict of Interest: None declared.

References

1 McKinlay JB. The worldwide prevalence and epidemiology of erectile dysfunction. Int J Impot Res 2000;12(Suppl. 4):506–11.
2 Litwin MS, Nied RJ, Dhanani N. Health-related quality of life in men with erectile dysfunction. J Gen Intern Med 1998;13:159–66.
3 Rust J, Golombok S, Collier J. Marital problems and sexual dysfunction: How are they related? Br J Psychiatry 1988;152:629–31.
4 NIH Consensus Development Panel on Impotence. NIH Consensus Conference. Impotence. JAMA 1993;270:83–90.
5 Wagner G, Fugl-Meyer KS, Fulg-Mejer AR. Impact of erectile dysfunction on quality of life: Patient and partner perspectives. Int J Impot Res 2000;12(Suppl. 4):144–6.
6 Fulg-Meyer AR, Lodnert G, Branholm JB, Fulg-Meyer KS. On life satisfaction in male erectile dysfunction. Int J Impot Res 1997;9:141–8.
7 Stiggelbout AM, de Haes JC. Patient preference for cancer therapy: An overview of measurement approaches. J Clin Oncol 2001;19:220–30.
8 Chen J, Mabjeesh NJ, Greenstein A. Sildenafil versus the vacuum erection device: Patient preference. J Urol 2001;166:1779–81.
9 Hatzichristou DG, Apostolidis A, Tzortzis V, Ioannides E, Yannakoyorgos K, Kalinderis A. Sildenafil versus intracavernous injection therapy: Efficacy and preference in patients on intracavernous injection from more than 1 year. J Urol 2000;164:1197–200.
10 Govier F, Potempa AJ, Kaufman J, Denne J, Kovalenko P, Ahuja S. A multicenter, randomized, double-blind, crossover study of patient preference for tadalafil 20 mg or sildenafil citrate 50 mg during initiation of treatment for erectile dysfunction. Clin Ther 2003;25:2709–23.
11 Ströberg P, Murphy A, Costigan T. Switching patients with erectile dysfunction from sildenafil citrate to tadalafil: Results of a European multicenter, open-label study of patient preference. Clin Ther 1993;25:2724–37.
12 Von Keitz A, Rajfer J, Segal S, Murphy A, Denne J, Costigan T, Lockhart D, Beasley CM Jr, Emmick JY. A multicenter randomized, double-blind, crossover study to evaluate patient preference between tadalafil and sildenafil. Eur Urol 2004;45:499–509.
13 Brock GB, McMahon CG, Chen KK, Costigant T, Sheen W, Watkins V, Anglin G, Whitaker E. Efficacy and safety of tadalafil for the treatment of erectile dysfunction: Results of integrated analyses. J Urol 2002;168:1332–6.
14 Saenz de Tejada I, Anglin G, Knight TR, Emmick JT. Effects of tadalafil on erectile dysfunction in men with diabetes. Diabetes Care 2002;25:2159–64.
15 Porst H, Padma-Nathan H, Giuliano F, Anglin G, Varanese L, Rosen R. Efficacy of tadalafil for the treatment of erectile dysfunction at 24 and 36 hours after dosing: A randomized controlled trial. Urology 2003;62:121–5.
16 Hatzichistou DG. Sildenafil citrate: Lessons learned from 3 years of clinical experience. Int J Impot Res 2000;14(Suppl. 1):543–52.
17 Hellstrom WJ, Gittelman M, Karlin G, Segerson T, Thibonnier M, Taylor T, Padma-Nathan H. Sustained efficacy and tolerability of vardenafil, a highly potent selective phosphodiesterase type 5 inhibitor, in men with erectile dysfunction: Results of a randomized double-blind, 26 week placebo-controlled pivotal trial. Urology 2003;61(Suppl. 1):8–14.
18 Goldstein J, Young JM, Fischer J. Vardenafil, a new phosphodiesterase type 5 inhibitor, in the treatment of erectile dysfunction in men with diabetes: A multicenter double-blind placebo-controlled fixed-dose study. Diabetes Care 2003;26:777–83.
19 Carson CC, Burnett AL, Levine LA, Nehra A. The efficacy of sildenafil citrate (Viagra) in clinical populations: An update. Urology 2002;60(Suppl. 2):12–27.
20 Moncada I, Jara J, Subira D, Castano I, Hernandez C. Efficacy of sildenafil at 12 hours after its intake: Reexploring the therapeutic window. Eur Urol Suppl 2003;2:95:(Abstract).
21 Hackett GJ. What do patients expect from erectile dysfunction therapy? Euro Urol Suppl 2002;1:4–11.
22 Jarow JP, Nana-Sinkam P, Sabbagh M, Eskew A. Outcome analysis of goal directed therapy for impotence. J Urol 1996;155:1609–12.
23 Althof SE, Corty EW, Levine SB, Levine F, Burnett AL, McVary K, Stecher V, Seftel AD. EDITS. Development of questionnaires for evaluating satisfaction with treatments for erectile dysfunction. Urology 1999;53:793–9.
24 Pommerville P. Erectile dysfunction: An overview. Can J Urol 2003;10(Suppl. 1):2–6.
25 Rosen RC, Riley A, Wagner G, Ostertoh IH, Kirkpatrick J, Mishra A. The international index of erectile function (IIEF): A multidimensional scale for assessment of erectile dysfunction. Urology 1997; 49:822–30.
26 Fink HA, MacDonald R, Rutks JR, Nelson DB, Wilt TJ. Sildenafil for male erectile dysfunction: A systematic review and meta-analysis. Arch Intern Med 2002;162:1349–60.
27 Marks LS, Duda C, Dorey FJ, Macairan ML, Santos PB. Treatment of erectile dysfunction with sildenafil. Urology 1999;53:19–24.

28 Goldstein I, Lue TF, Padma-Nathan H, Rosen RC, Steers WD, Wicker PA. Oral sildenafil in the treatment of erectile dysfunction. N Engl J Med 1998; 338:1397–404.
29 Hellstrom WJ, Gittelman M, Karlin G, Segerson T, Thibonnier M, Taylor T, Padma-Nathan H, On behalf of the Vardenafil Study Groups. Vardenafil for treatment of men with erectile dysfunction: Efficacy and safety in a randomized, double-blind, placebo-controlled trial. J Androl 2002;23:763–71.
30 Porst H, Young JM, Schmidt AC, Buvat J. Efficacy and tolerability of vardenafil for treatment of erectile dysfunction in patient subgroups. Urology 2003;62:519–23.
31 Hatzichristou D, Montorsi F, Bovat J, Laferriere N, Bandel TJ, Porst M. The efficacy and safety of flexible-dose vardenafil (levitra) in a broad population of European men. Eur Urol 2004;45:634–41.
32 Carson CC, Rajfer J, Eardley I. The efficacy and safety of tadalafil: An update. Br J Urol Int 2004;93:1276–81.
33 Porst H, Padma-Nathan H, Giuliano F, Anglin G, Varanese L, Rosen R. Efficacy of tadalafil for the treatment of erectile dysfunction at 24 and 36 hours after dosing: A randomized controlled trial. Urology 2000;164:121–5.
34 Giuliano F, Montorsi F, Mirone V, Rossi D, Sweeney M, For the Sildenafil Multicenter Study Group. Switching from intracavernous prostaglandin E1 injections to oral sildenafil citrate in patients with erectile dysfunction: Results of a multicenter European study. J Urol 2000;164:708–11.
35 Shabsigh R, Padma-Nathan H, Gittleman M, McMurray J, Kaufman J, Goldstein I. Intracavernous alprostadil alfadex (EDEX/VIRIDAL) is effective and safe in patients with erectile dysfunction after failing sildenafil (Viagra). Urology 2000;55: 477–80.
36 Buvat J, Colson MHC, Lemaire AL, Bou-Jaoude GB, Alexandre BA. Real world experience with tadalafil in 300 ED patients. J Sex Med Suppl 2004; 1:79.
37 Hammadeh M, Kwong Y, Araya M. Efficacy, safety and patient preference of tadalafil (Cialis) in men with erectile dysfunction. J Sex Med Suppl 2005;1:58.
38 Yaman O, Turkey;Ghlosta P, Konalev V, Shenfeld O, Pack D, Breza J, Clarke P, Kopernicky V. Switching from sildenafil (Viagra) to tadalafil (Cialis) in men with erectile dysfunction in central/eastern European and eastern Mediterranean regions: Assessment of sexual attempt behavior and psychological and interpersonal relationship scales. J Sex Med Suppl 2005;1:65.
39 Porst H, Kleingarn M, Arnds S. The two PDE-5 inhibitors sildenafil and tadalafil: Results of an independent intraindividual comparative trial. Eur Urol Suppl 2004;3:27.
40 Claes HIM, Van Poppel H. The use of sildenafil, tadalafil and vardenafil in clinical practice. J Sex Med Suppl 2004;1:42.
41 Pakh NC, Park HJ, Nam JK, Kim JM. Efficacy and side effects of the PDE-5 inhibitors sildenafil, vardenafil and tadalafil: Results of open label study of patient preference in Korea. J Sex Med Suppl 2005;1:35.
42 Porst H, Keingarn M, Arnos E. The three PDE-5 inhibitors sildenafil, tadalafil and vardenafil. Results of a comparative preference trial in 222 patients with erectile dysfunction. J Urol 2004;171(4 Suppl):315.
43 Porst H. The 3 PDE-5 inhibitors sildenafil, tadalafil and vardenafil in patients with diabetes and ES—Results of a comparative trial in 107 patients. J Sex Med Suppl 2005;1:21.
44 Sommer F, Mathers M, Klotz T, Bondarenko B, Caspers HP, Engelmann V. Which PDE-5 inhibitors do patients prefer? A comparative study of 50 mg Sildenafil, 10 mg Tadalafil and 10 mg Vardenafil. Eur Urol Suppl 2004;3:105.
45 Sommer F, Klotz T, Mathers M, Bondarenko B, Caspers HP, Engelmann V. A comparative randomised multicenter study of the maximum dose of sildenafil, tadalafil and vardenafil. Eur Urol Suppl 2004;3:105.
46 Stoberg P, Ljunggren CRN, Hedeling H. Patient preference in clinical practice in treatment of erectile dysfunction with PDE-5 inhibitors. J Sex Med Suppl 2004;1:41.