

Original Article

Patterns of treatment with PDE5 inhibitors in the clinical practice in Italy: longitudinal data from the Erectile Dysfunction Observational Study

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Abstract

The Erectile Dysfunction Observational Study (EDOS) is a 6-months observational prospective multicentric study enrolling men with erectile dysfunction (ED) who asked, to be started on a treatment or to change a previous treatment. Aims of the study were to analyse the pattern of treatment and compare the efficacy of treatments used. Patients were enrolled during a normal hospital visit and were prescribed a treatment for ED. They were asked at baseline and after 3 and 6 months, to answer a set of questions from the International Index of Erectile Function, Erectile Dysfunction Inventory of Treatment Satisfaction (EDITS) and Short Form of the Psychological and Interpersonal Relationships Scale questionnaires (SF-PAIRS). Clinicians were free to prescribe any therapy for ED available in the market, and to change therapy at any time during the study. Out of 1 338 patients, available for analysis at 6 months, 624 (47%) changed their treatment during the study and 714 (53%) continued with the drug prescribed at baseline. Patients assuming tadalafil had a significantly higher probability of maintaining the same treatment compared to sildenafil or vardenafil. There was no clinically significant difference in terms of efficacy, patient satisfaction, self-confidence and spontaneity between the different inhibitors of PDE5. The ‘time concerns’ domain score of SF-PAIRS, was statistically better in patients assuming tadalafil. In conclusion sildenafil, vardenafil and tadalafil show similar efficacy in the clinical practice. However, patients receiving tadalafil display a lower risk to discontinue or change the treatment.

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1 Introduction

Phosphodiesterase type 5 inhibitors (PDE5) represent the current, first-line therapy in the treatment of erectile dysfunction (ED), independent of severity and etiology. The three compounds available on the

market today, that is, sildenafil, tadalafil and vardenafil, have shown an overlapping profile of efficacy, safety and tolerability in a number of controlled trials [1–8]. Each of these compounds offers particular pharmacokinetic characteristics: the time necessary to reach the peak plasma level is about 1 h with sildenafil and vardenafil, and about 2 h with tadalafil, according to the official Summary of Product Characteristics (SPC) of the three PDE5 inhibitors (PDE5i's), as approved by European Medicines Agency; food and alcohol can delay the action of sildenafil and the absorption of vardenafil, but do not interfere with tadalafil; the plasma half-life is 4–5 h for sildenafil and vardenafil and 17.5 h for tadalafil [9–11].

The need to optimize the treatment of ED, making full use of the characteristics of the three compounds, has led several researchers to carry out comparison and preference studies [12–16]. The choice of drug for a particular patient not only depends on the efficacy, safety and tolerance of the treatment but also on the quality of communication between the patient and the doctor, and between the man and his partner; on the awareness, correct or incorrect, that the patient has of ED drugs; on the motivation and the therapeutic expectations of the patient and his partner; on the spontaneity and self-confidence that goes with the sexual act; and on the impact on quality of life in general [17–20]. Comparison and preference studies present different methodological problems. A comparison study between PDE5i's can be carried out only with a double-blind randomized crossover design, which reduces all possible errors to the minimum [21]. The majority of studies published today do not meet these criteria in full; therefore, the observations that originate from them should be applied to clinical practice with great care [22]. Moreover, the doctor-patient dynamics, which impact on the choice of drug in the context of clinical practice, often move away from the strict criteria used in comparison trials.

In clinical practice, PDE5i's are prescribed electively from the point of view of the doctor and the patient, and during the course of control visits, variation of the dosage of the particular drug is based on the efficacy, side effects and patient satisfaction judged from whether the therapy corresponds to the patient's requirements and expectations. This type of therapeutic approach, although universally used, has never been accurately described. The reasons for choosing to follow the same treatment, to change it or abandon it

for a different treatment have also not been described.

The Erectile Dysfunction Observational Study (EDOS) is a 6-month multicenter prospective observational study carried out in nine European countries, enrolling patients affected by ED who have been referred for treatment. The study was carried out in clinical practices and the doctors were free, not only to prescribe one of the three PDE5i's, namely, sildenafil, tadalafil and vardenafil but also to change treatment one or more times at any time during the 6-month study; they could choose either one of the PDE5i's or alternative treatment, such as, intracavernous alprostadil or the vacuum device. The results of the whole study were recently disclosed [23].

The Italian data from EDOS can now be used to describe, for the first time, the pattern of treatment for ED in the context of clinical practice in Italy, to compare the efficacy of different treatments, to identify the factors that influence the choice of continuing with the original drug or changing to another during the course of the following months.

2 Materials and methods

Men who were aged 18 years or over and had asked their general practitioners (GP) or specialist to start them on a course of treatment for ED or to change an existing treatment were enrolled. Patients already involved in other drug trials could not be enrolled. The study protocol was approved by the relevant ethical committees from all the participating centers.

Patients were enrolled during a normal hospital visit (visit 1), during which they signed an informed consent form and were given their first prescription, to begin their treatment for ED or change a treatment already started. Investigators were suggested, but not required, to prescribe one of the treatments available for ED in order to have about 50% of patients receiving tadalafil and the remaining 50% taking any other treatment. The patients were re-evaluated after 3 months (visit 2) and 6 months of treatment (visit 3). In accordance with the purely observational design of the study, the researchers were given no instruction with regard to the therapeutic approach; the choice and the prescription of the drug during visit 1 followed the normal routine of each center, and proper instructions on the use of each drug were given according to the normal clinical practice and patient information leaflets. The doctor and patient could decide at any time to vary the dosage of the drug

or to change to an alternative treatment, including injected drugs. Patients who continued the initial treatment till visit 2 were defined as ‘completers to T2’; completers to T2 who continued the initial treatment till visit 3 were defined as ‘completers to T3’.

During visit 1, demographic (age, body mass index [BMI], conjugal state), socio-economic and educational data were collected for each patient, and a complete clinical history was taken, including information on smoking habits, alcohol consumption, any comorbidity, concomitant use of antidepressives, antihypertensives, hypolipidemics, antipsychotics, chemotherapy and cardiovascular drugs in general. The researching doctor had to collect data on the characteristics of the ED, on the coexistence of disturbances of desire and ejaculation and the eventual treatments, and he had to make a judgement on the degree of severity of the illness (light, moderate, severe ED) using the International Index of Erectile Function-Erectile Function (IIEF-EF) domain score.

During visit 1, and on visits 2 and 3, each patient privately answered a set of questions aimed at estimating the efficacy of the treatment, sexual satisfaction and some psychological aspects on their interpersonal relationship:

1) Measures of efficacy:

- Question 6 of IIEF (number of relationships attempted)
- Single-item question (SIQ) 1 (has it happened in last the 6 months that your erection has been insufficient to begin or to complete the relationship?);
- SIQ 2 (has the therapy that you have been taking resolved your problem?);
- Global Assessment Question (GAQ) 1 (has the therapy that you have been taking in the last 4 weeks improved your erectile function?);
- GAQ 2 (has this treatment has improved your ability to undertake sexual activities?);
- Question: what has been the maximum time between taking the drug and the moment when you have been able to undertake the relationship?

2) Measures of sexual satisfaction:

- Question 7 of IIEF (satisfaction with sexual relationship);
- Question 14 of IIEF (satisfaction with sexual relationship with partner);
- Question 1 of the Erectile Dysfunction Inventory of Treatment Satisfaction (EDITS) questionnaire (total satisfaction);

3) Physiological and relational aspects:

- Short Form Questionnaire Psychological and Interpersonal Relationship Scale (SF-PAIRS): eight questions on time concern; four questions on spontaneity; three questions on self-confidence.

Efficacy measures are described in section 2.2.

The data collected were used to (a) analyze the pattern of treatment, identifying the factors that influenced the decision to continue throughout the study with the start drug or change it during the following months; (b) compare the ‘efficacy’ of the drugs used.

2.1 *Analysis of treatment patterns*

By comparing the baseline characteristics of the completers and non-completers, it was possible to estimate the predictivity of numerous variables on the decision to continue with the initial treatment or change during the course of the study. The variables analyzed were: characteristics of ED; age; BMI; conjugal status; education and socio-economic status of the patient; disturbances of desire and ejaculation; consumption of alcohol and cigarettes; various co-morbidities and co-administration of drugs; and the treatment prescribed at the start of the study.

2.2 *Comparison of efficacy*

Completers represent a subgroup suitable for comparison of the efficacy of the different drugs used in clinical practice through the following parameters:

(a) Two unique, single-item questions (SIQ1 and SIQ2) and two global assessment questions (GAQs) at baseline, V2 and V3; in the SIQs, the patient was asked whether his erection during the past 4 weeks had been insufficient to initiate or complete the intercourse (SIQ1) and then whether the treatment he had been taking in the past 4 weeks solved the problem (SIQ2); the GAQs asked whether the treatment the patient received improved his erections (GAQ1), and if so, whether the treatment improved his ability to engage in sexual activity (GAQ2);

(b) question 7 and 14 of the IIEF to assess intercourse satisfaction and satisfaction with sexual relationship with partner, respectively;

(c) question 1 of the EDITSPsychological and Interpersonal Relationship Scale) questionnaire to assess overall satisfaction;

(d) the SF-PAIRS questionnaire to assess patient’s sexual self-confidence, spontaneity and time concerns. Furthermore, at the end of the study, patients answered

the question ‘About what was the longest amount of time that the most recently taken ED treatment remained effective, during the last month, from taking it to attempting intercourse?’

2.3 Statistical methods

Estimates of continuous variables are reported as means and standard deviations. For categorical data, the number and percentage of the total are reported. All estimates are based on non-missing data.

The efficacy of treatment was analyzed using multivariate modeling techniques to adjust the treatment effects by baseline characteristics, which were found to be statistically associated with the outcome measure of interest.

Analysis of Covariance model was used to report adjusted mean differences for continuous outcome measures (SF-PAIRS, IIEF Q6 and interval between taking the drug and last attempt at sexual intercourse). A logistic regression model was used for binary outcome measures (GAQ1, GAQ2, IIEF Q7 and Q14, EDITS and SIQ1 and SIQ2).

Baseline factors selected for the models were identified first, using a stepwise reduction method at the 5% level of significance. Having identified the baseline factors for inclusion, a second model was developed, which included treatment and the significant baseline factors. The baseline value of the outcome measure was included in the models for the continuous outcome measures where appropriate.

Effect size statistics to assess clinical significance were calculated from the adjusted means belonging to the continuous models.

The likelihood of patients continuing on their baseline treatment was analyzed using a univariate and multivariate approaches.

The baseline characteristics were compared in the two groups: completers or non-completers. The categorical variables were compared by contingency tables and χ^2 -tests or Fisher’s exact tests. The numerical variables were analyzed using a comparison of means (analysis of variance, ANOVA).

A logistic regression has been used for the adjusted models, testing the probability of maintaining the same medication. The first model was run with all the baseline characteristics using a stepwise reduction method at 0.05%. Then, the second model was run, including the variables that resulted significant from the first model. When it was not possible to use a stepwise

reduction method, a backward reduction method was applied at the level 0.15.

Only statistically and clinically relevant results are highlighted in this paper.

3 Results

3.1 Patients

Between April 2003 and April 2004, 1 419 patients were enrolled from 129 Italian centers involved in EDOS and were prescribed a treatment for ED. A total of 1 366 patients (mean age 55.0 years [range 19–81 years]; BMI 26.8 [range 17.6–44.2]) were eligible for analyses at 3 months. The baseline characteristics of this group have been described earlier and reflect characteristics of Italian population of patients affected by ED [24]. Briefly, patients presented with psychogenic, organic and mixed ED in 23.7%, 33.5% and 42.8% of cases, respectively. As many as 444 (32.5%) patients were non-naïves for ED treatment; 266 of them had a known therapy for ED in the 4 weeks before study initiation: 126 (47.4%) were using sildenafil, 47 (17.7%) a combination therapy, 41 (15.4%) other therapies, 29 (10.9%) vardenafil and 23 (8.6%) tadalafil.

During the study, 446 patients (33%) changed initial treatment, 898 (65.7%) continued with the drug prescribed at baseline (completers at T2). Of the 1338 patients available for analysis at 6 months, 624 (46.6%) changed to another treatment during the study and only 714 (53.3%) continued with the drug prescribed at baseline (completers at T3). Percentages of completers divided for initial treatment were the following: 535 out of the 879 who had started with tadalafil (60.9%), 75 out of the 171 starting with sildenafil (43.9%), 66 out of the 152 starting with vardenafil (43.4%) and 38 out of the 136 starting with other treatments (27.9%). It is to be noted that on dividing the patients according to their initial treatment (tadalafil, sildenafil, vardenafil and others), the baseline characteristics were found to be similar among the groups (Table 1).

3.2 Patterns of treatment

In both the univariate and multivariate analysis, the most influential factor for the decision to continue or change the initial treatment was the drug prescribed at baseline. In the logistic regression model, patients treated with tadalafil had a statistically significant higher probability ($P < 0.001$) of maintaining the same

treatment compared with those treated with sildenafil at 3 months and with sildenafil or vardenafil at 6 months (Figure 1).

From the univariate analysis, other variables negatively influencing the probability of continuing with the initial treatment at 6 months were history of

Table 1. Baseline characteristic of patient ‘completers’.

	Tadalafil (n = 535)	Sildenafil (n = 75)	Vardenafil (n = 66)	Others (n = 38)
Age (years, mean ± SD)	53.8 ± 11.7	53.4 ± 12.0	55.7 ± 10.7	59.1 ± 10.4
Naive for ED treatment (n [%])	366 (68.4)	58 (77.3)	47 (71.2)	24 (63.2) [#]
Etiology (n [%])				
Psychogenic	139 (26.0)	19 (25.3)	21 (31.8)	3 (7.9) [*]
Organic	163 (30.5)	21 (28.0)	13 (19.7)	22 (57.9) [*]
Mixed	231 (43.2)	35 (46.7)	32 (48.5)	13 (34.2) [*]
Duration of ED >1 year (n [%])	294 (54.9)	41 (54.7)	46 (69.7)	19 (50) [§]
IIEF-EF total score (mean ± SD)	14.4 ± 7.0	16.4 ± 6.4	15.7 ± 7.2	11.3 ± 7.3
Severity assessed by the investigator (n [%])				
Mild	119 (22.2)	15 (20.0)	18 (27.3)	6 (15.8) [§]
Moderate	292 (54.6)	49 (65.3)	41 (62.1)	14 (36.8) [*]
Severe	120 (22.4)	11 (14.7)	7 (10.6)	18 (47.4) [*]
Stable relationship (n [%])	469 (87.7)	69 (92.0)	57 (86.4)	35 (92.1)

Abbreviations: IIEF-EF, International Index of Erectile Function-Erectile Function-Erectile Function;

^{*}P < 0.05, compared with tadalafil, sildenafil and vardenafil;

[§]P < 0.05, compared with vardenafil.

[#]P < 0.05, compared with sildenafil.

Other values were comparable among the groups.

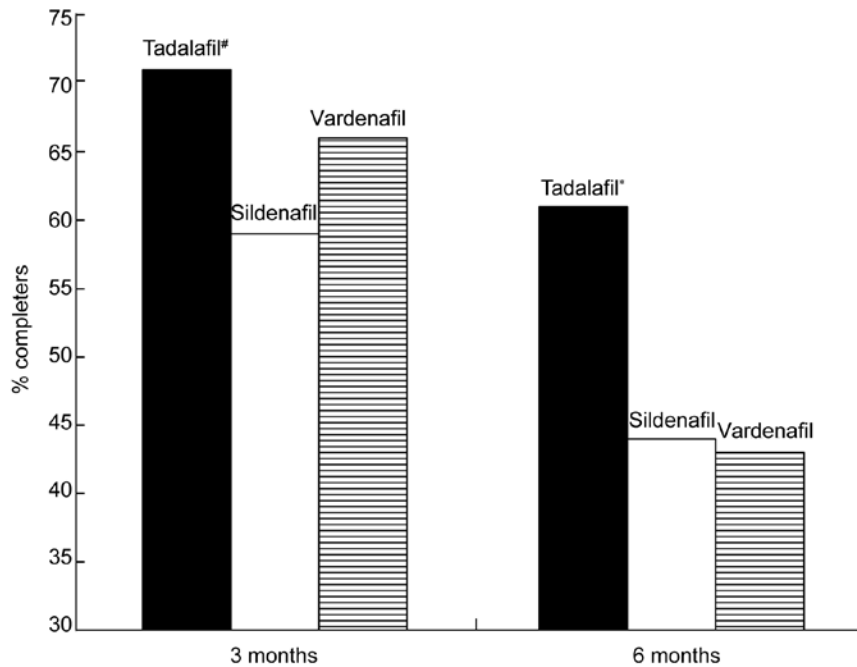


Figure 1. Percentage of completers according to their start treatment. [#]P < 0.001, P = 0.346, compared with sildenafil and vardenafil, respectively; ^{*}P < 0.0001, compared with sildenafil and vardenafil, respectively.

radical prostatectomy ($P = 0.042$), lessening of desire ($P = 0.043$), being non-naive for PDE5i's ($P = 0.048$) among the categorical variables (Table 2), and advanced age of patient ($P = 0.01$) and great severity of ED according to IIEF ($P = 0.0001$) among the continuous variables (Table 3). From the multivariate analysis, the only factors predicting 6-month completion besides the treatment group were severity of ED ($P = 0.001$) and sexual desire ($P < 0.027$).

3.3 Efficacy of treatment

There were no clinically significant differences in terms of efficacy, patient satisfaction, self-confidence and between the different PDE5i's. At 6 months, but not at 3 months, spontaneity was improved significantly more with vardenafil than with sildenafil. No differences

were found comparing tadalafil with both vardenafil and sildenafil.

At the 6-month stage, the score for the 'time concerns' domain of SF-PAIRS was statistically better for those patients who had taken tadalafil compared with those using other treatments (adjusted least square means 2.12 for the tadalafil group, 2.27 for vardenafil and 2.41 for sildenafil; Table 4). The difference between sildenafil and tadalafil is clinically significant at the effect size test.

Time-lapse between taking the drug and a sexual intercourse was over 12 h in 9% of patients treated with sildenafil or vardenafil and in 55% of patients using tadalafil; no patient taking sildenafil or vardenafil reported an interval superior to 24 h, whereas 28% of patients taking tadalafil did (Figure 2).

Table 2. Categorical predictive variables at baseline for the completers to 6 months (higher percentages indicates higher possibility of completion).

		Non-completers to 6 months, <i>n</i> (%)	Completers to 6 months, <i>n</i> (%)	<i>P</i> -values (χ^2)
Radical prostatectomy	No	542 (45.6)	646 (54.4)	0.042
	Yes	73 (54.9)	60 (45.1)	
Reduced sexual desire	No	439 (45.0)	537 (55.0)	0.043
	Yes	178 (51.3)	169 (48.7)	
Naive/non-naive at baseline	Non-naive	219 (50.5)	215 (49.5)	0.048
	Naive	400 (44.7)	495 (55.3)	

Table 3. Continuous predictive variables at baseline for the completers to T3.

	Mean age in years (SD)	Mean IIEF-EF score (SD)
Non-completers	55.87 (11.36)	13.10 (7.03)
Completers	54.24 (11.65)*	14.57 (7.01) [#]

Two-way ANOVA test: * $P = 0.01$, [#] $P = 0.0001$, compared with non-completers.

Table 4. Short Form Questionnaire Psychological and Interpersonal Relationship Scale (SF-PAIRS) score for time-concern domain after 6 months of treatment.

Comparison between treatments	Δ SF-PAIRS time-concern: mean (95% CI)	Pr > <i>t</i>
Vardenafil vs. tadalafil	0.1504 (0.009–0.292)	0.0062*
Sildenafil vs. tadalafil	0.2880 (0.154–0.422)	< 0.0001* [§]
Other treatment vs. tadalafil	0.3067 (0.118–0.496)	< 0.0001*
Vardenafil vs. sildenafil	-0.1377 (-0.321–0.045)	0.0523
Other vs. sildenafil	0.0187 (-0.204–0.241)	0.8280
Vardenafil vs. other treatment	-0.1564 (-0.383–0.070)	0.0754

*Statistically significant.

[§]Clinically significant for the 'effect size test'.

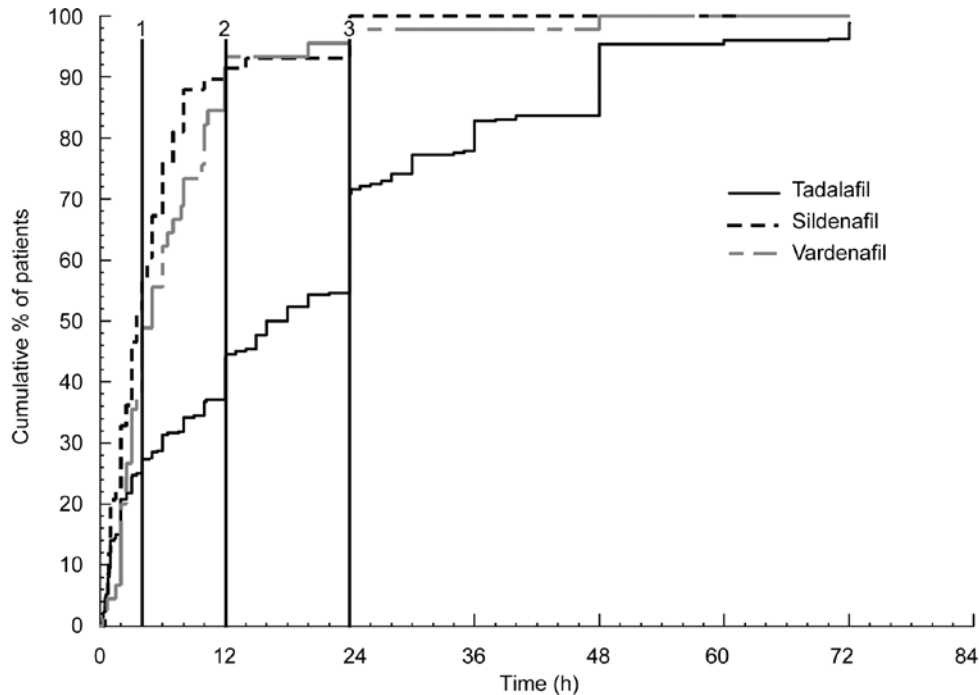


Figure 2. Cumulative percentage of patients who were unable to attempt sexual intercourse after 4 h (Line 1) (sildenafil and vardenafil vs. tadalafil; $P < 0.05$), 12 h (Line 2) (sildenafil and vardenafil vs. tadalafil; $P < 0.01$) and 24 h (Line 3) (sildenafil and vardenafil vs. tadalafil; $P < 0.01$). Data reported by patients answering the question ‘about what was the longest amount of time that the most recently taken ED treatment remained effective, during the last month, from taking it to attempting intercourse?’.

Nothing is known of the patients who were lost to follow-up. Among the baseline variables, only the low level of education and depression were predictors of dropout from the study.

4 Discussion

The results of observational studies can be considered to complement those of randomized controlled trials. Observational studies usually have higher external validity, because the samples are more representative of the daily practice population, whereas randomized controlled trials have higher internal validity because of their design accuracy and standardized procedures [25]. Although many clinical trials have shown a substantial equivalence between the three inhibitors, in terms of efficacy, tolerability and sexual satisfaction [1–8], this observational study, lasting 6 months and carried out in the context of daily clinical practice, suggests that there is a perceptible difference between the three drugs in the ‘true life’ setting.

These results confirm that sildenafil, tadalafil and

vardenafil are all very effective, with comparable results in all the efficacy measures used. Even from the point of view of sexual satisfaction, no significant differences were found between the three inhibitors. Nonetheless, around half of the patients in the 6-month study period were not completers at 6 months. It is important to note that the analysis of efficacy was carried out on completer patients and not on those who changed treatment before the first follow-up visit. It is not possible, therefore, to evaluate the efficacy and satisfaction of patients who changed treatment/did not complete (non-completers). An analysis of ‘intention to treat’ would be necessary if we wanted to interpret this study as a ‘comparison study’ between the PDE5i’s. On analyzing the basal characteristics of the study population, it emerges that only a few variables influence the probability of maintaining or changing the initial treatment, the main one being the drug prescribed at baseline. The patients who were given tadalafil continued the initial treatment more often than those who were given sildenafil or vardenafil.

One aspect for which tadalafil showed results

that were significantly different from sildenafil and vardenafil was the maximum interval reported between taking the drug and a sexual intercourse.

The SF-PAIRS score showed clinically comparable results for the three inhibitors in the areas of spontaneity and self-confidence. In the domain of time concern (a measure of the preoccupation on the need to plan a sexual relation in the window of efficacy of the drug and to complete it before the effect disappears), however, tadalafil showed a significantly greater statistical and clinical superiority.

The data from this study confirm that (1) from the point of view of efficacy and sexual satisfaction, sildenafil, tadalafil and vardenafil gave equivalent results for all the measures used, although tadalafil, which gives a greater time interval between consumption and sexual relations, is significantly better in the time-concern domain from the SF-PAIRS questionnaire; (2) in the context of clinical practice, in which it was possible to freely change treatment, compliance to PDE5i's was higher compared with other treatments, that were discontinued more frequently. Among patients treated with PDE5i's, those who were given tadalafil continued with the same drug more often than patients who were given sildenafil or vardenafil; (3) in the clinical practice, different patterns of treatment were observed with sildenafil, vardenafil and tadalafil for ED, although no major difference were reported in terms of efficacy, satisfaction or safety. In particular, a greater number of patients confirmed tadalafil at a 6-month follow-up. The longer stay in treatment of patients taking tadalafil may be linked with the improvement of the time-concern domain. However, this single observational study alone is not sufficient to confirm this statement, and further observational studies as well as prospective comparative trials are warranted.

Other authors carried out a similar analysis on patients from the total EDOS database, which covers more than 8 000 patients enrolled in several European countries. Even with possible limitation due to physician's assignment to ED treatment, that may be influenced by the sponsorship of the trial, they reported that tadalafil was (1) more effective than sildenafil and vardenafil; (2) statistically superior to sildenafil and vardenafil with respect to questions 7 and 14 of the IIEF-EF questionnaire (measure of satisfaction) [23]. This superiority has not been confirmed in the Italian subset, putting into perspective the role of sexual satisfaction in determining the different permanence in

treatment of patients treated with the three inhibitors. The greater percentage of patients who stayed on treatment, therefore, could be considered a sign of the greater ability of tadalafil to correspond to the real needs of most patients, which are not detected or noticed in the commonly used efficacy and satisfaction measures.

In the treatment of ED in clinical practice, some basal variables of the patient, his clinical history and the characteristics of his ED, influence the patient's choice to follow the initial drug or change to an alternative treatment. Patients initially prescribed to take tadalafil continued the treatment in a significantly higher number of cases compared with those given sildenafil and vardenafil. The three PDE5i's do not seem to offer substantial differences in terms of efficacy and sexual satisfaction. However, tadalafil offers greater duration of action, which leads to a better impact on the preoccupation of having to plan sexual relations during the window of efficacy of the drug and to complete it before the effect disappears. This characteristic seems to be the determinant for the patient's choice to maintain the initial treatment.

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Appendix

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