

· *Clinical Experience* ·

Evaluation of an alternative dosing regimen with tadalafil, three times per week, for men with erectile dysfunction: SURE study in Italy

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Abstract

Aim: To examine the preference for two dosing regimens of 20 mg of tadalafil, on demand or three times per week, in men affected with erectile dysfunction (ED) in Italy. **Methods:** Scheduled Use versus on demand Regimen Evaluation (SURE) is a multicenter, crossover and open-label study, involving 94 urology centers in Italy. Patients aged 18 years or older affected with ED for at least 3 months were enrolled and randomized to 20 mg of tadalafil treatment on demand or three times per week for 5–6 weeks. After a 1-week washout, patients were crossed over to the alternate regimen for 5–6 weeks. A treatment preference question was used to determine the preferred treatment regimen. International Index of Erectile Function (IIEF) and Sexual Encounter Profile (SEP) questionnaire were used as efficacy measures. **Results:** A total of 1 058 men (mean age 54.8 years), were randomized to treatment. Overall, 59.1% of patients preferred the on-demand regimen and 41.9% preferred the three times per week dosing. Both regimens were efficacious and well tolerated. Although a statistically higher improvement of the IIEF erectile function (IIEF-EF) domain score and the SEP questionnaire was reported for the three times per week compared to the on-demand treatment regimen, this difference was numerically minimal and lacking in clinical significance. **Conclusion:** Tadalafil is effective and well tolerated whether used on demand or three times per week. Patients should be given the option to choose the best treatment regimen according to personal needs and preferences. (*Asian J Androl* 2007 May; 9: 395–402)

Keywords: erectile dysfunction; SURE study; on demand; three times per week; alternate; tadalafil

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Received 2006-06-08 Accepted 2006-06-15

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1 Introduction

Tadalafil is an effective and well tolerated phosphodiesterase type 5 (PDE5) inhibitor, approved in more than 100 countries for the treatment of erectile dysfunction (ED). Compared to sildenafil citrate and vardenafil HCL, tadalafil presents unique pharmacokinetic properties, as it has been shown to be effective up to 36 hours from dosing [1]. This characteristic has opened new therapeutic possibilities in the treatment of ED with respect to other shorter half-life PDE5 inhibitors that allow patients to engage in sexual intercourse within a few hours of dosing. Using traditional “on-demand” dosing, the long-lasting effectiveness of tadalafil allows patients to engage in sexual intercourse far after dosing, reducing the need for strictly planning sexual activity [2].

Furthermore, dosing of tadalafil on a regular basis has been evaluated. The Scheduled Use versus on demand Regimen Evaluation (SURE) study, including more than 4 000 patients in 14 European countries, has demonstrated that a three-time per week regimen of tadalafil is as effective and well tolerated as the on-demand regimen and that more than 42.2% of patients prefer the fixed dosing treatment when allowed to choose [3]. However, the pattern of choice was independent of patients’ baseline characteristics, like ED severity and etiology and the reasons for preference were related to individual cultural and psychosocial factors, which might differ among countries. We analyzed the Italian data subset of the SURE study to evaluate the efficacy and safety of a fixed dosing treatment with 20 mg of tadalafil and to determine patient preference for an on-demand or a three-time per week regimen.

2 Materials and methods

SURE was a randomized, crossover and open-label

study, involving 94 urology centers in Italy from October 2002 to July 2003. Patients were included if aged at least 18 years and affected with ED of any severity and etiology for at least 3 months. Patients had to be engaged in a stable heterosexual relationship throughout the study period and had to agree not to use any other ED treatment from the beginning of the run-in period to 96 hours after the final visit. Exclusion criteria were: use of nitrates, cancer chemotherapy or antiandrogens and congestive heart failure. Notably, patients previously assuming other commercially available PDE5 inhibitors were not excluded from the study.

The study design (Figure 1) has already been described in detail [2]. Briefly, after signing an informed consent, each patient underwent a screening evaluation, including a comprehensive review of medical history, physical examination, laboratory safety tests and electrocardiogram, and started a 3–4 week run-in, treatment-free period phase. Patients were then randomized to assume 20 mg of tadalafil according to either a “on-demand” or “three times per week” regimen for 5–6 weeks (Treatment I). Patients did not have to observe any restriction on food or alcohol. Patients randomized to the “on-demand” regimen were instructed not to exceed one dose per day. Patients randomized to the “three times per week” regimen were instructed to assume 20 mg of tadalafil on Monday, Wednesday and Friday (subgroup A) or on Tuesday, Thursday and Saturday (subgroup B) at the same hour, independently of sexual activity. After a 1-week washout period, patients were switched to the other treatment regimen for 5–6 weeks (Treatment II), in a cross-over fashion. At the completion of the second treatment phase, patients were asked to choose the treatment regimen for the extension phase, which was for a required duration of at least 14 days.

Efficacy measures were the International Index of Erectile Function (IIEF) and the Sexual Encounter Profile (SEP) questionnaires, collected for each patient at the baseline and at the end of each treatment phase. As a preference measure, at the end of the second treatment phase patients were also asked to answer the Treatment Preference Question (TPQ): “Which treatment regimen did you prefer?” The options were on demand or scheduled (three times per week).

Treatment emergent adverse events, defined as events that first occurred or worsened after the baseline, were recorded throughout the study period, and all randomized patients were included in the safety analysis.

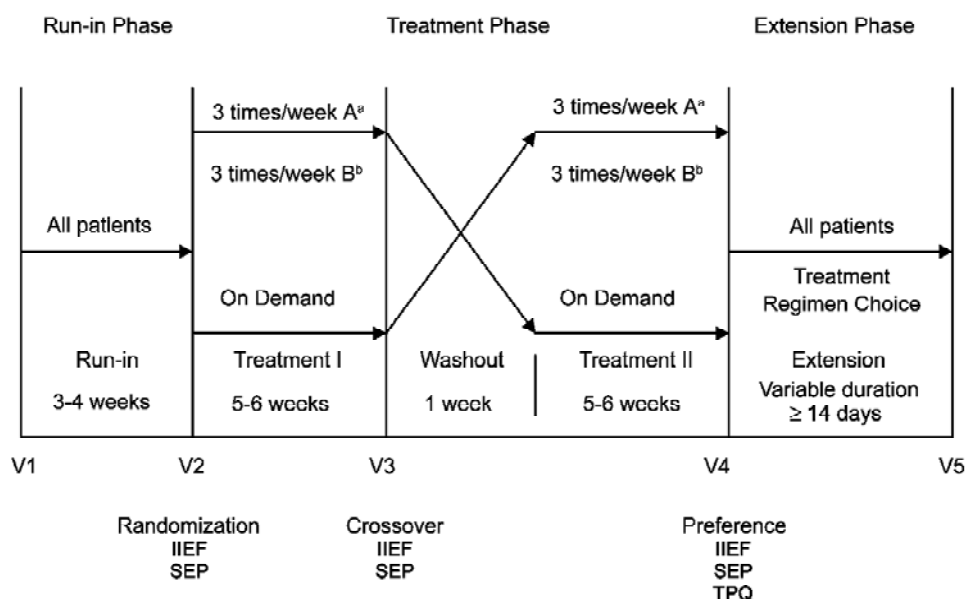


Figure 1. Study design. ^a Study medication (20 mg of tadalafil) taken Monday, Wednesday and Friday; ^b Study medication (20 mg of tadalafil) taken on Tuesday, Thursday and Saturday. IIEF, International Index of Erectile Function; SEP, Sexual Encounter Profile; TPQ, Treatment Preference Question.

Table 1. Summary of reason for study discontinuation during active therapy period by treatment regimen. D/SCH, treatment sequence on demand regimen (D) then three times per week regimen (SCH); SCH/D: treatment sequence SCH then D.

Status	D/SCH	SCH/D	Total
	N = 521 (n [%])	N = 537 (n [%])	N = 1058 (n [%])
Protocol completed	455 (87.3)	466 (86.8)	921 (87.1)
Adverse event	22 (4.2)	27 (5.0)	49 (4.6)
Lack of efficacy, patient perception	14 (2.7)	10 (1.9)	24 (2.3)
Unable to contact patient (lost to follow up)	10 (1.9)	9 (1.7)	19 (1.8)
Personal conflict or other decision of patients	18 (3.5)	21 (3.9)	39 (3.7)
Physician decision	2 (0.4)	2 (0.4)	4 (0.4)
Protocol violation	0	2 (0.4)	2 (0.2)

Statistical analyses were conducted on an intent-to-treat basis, considering TPQ as the primary endpoint and efficacy measures IIEF and SEP as secondary endpoints. The one-sample z-test with a two-sided significance of 0.05 was used to analyze the null hypothesis that equal proportions of patients prefer the on-demand and three times per week dosing regimens of tadalafil at the TPQ. Efficacy variables were evaluated by a cross-over analysis of variance model, using $P < 0.05$ as a cut-off for statistical significance. Protocol and informed consent documents were approved by ethical review board at each investigative site. The study was conducted in accordance with the protocol, the ethical principles stated

in the Declaration of Helsinki 2002 and applicable laws.

3 Results

3.1 Patients

Out of 1 140 Italian patients signing the informed consent, 1 058 completed the run-in phase and were randomized to treatment. All patients answered the preference question at the end of the second treatment phase. A total of 137 patients discontinued the study early (Figure 2). The most common reasons for early discontinuation were adverse events (4.6%) and lack of efficacy (2.3%) (Table 1).

Table 2. Patient baseline characteristics. †Based on IIEF-EF domain scores at baseline. ED, erectile dysfunction; EF, erectile function; IIEF, International Index of Erectile Function; SEP, Sexual Encounter Profile.

Characteristic	
Age (mean ± SD)	54.8 ± 10.5
Weight (kg) (mean ± SD)	80.3 ± 11.6
Height (cm) (mean ± SD)	172.9 ± 6.9
Race/ethnicity (n [%])	
Caucasian	1 057 (99.9)
African descent	1 (0.1)
Current smokers (n [%])	274 (25.9)
Current alcohol consumers (n [%])	431 (40.7)
ED severity† (n [%])	
Mild	436 (41.7)
Moderate	293 (28.0)
Severe	316 (30.2)
ED etiology (n [%])	
Organic	366 (34.6)
Mixed	485 (45.8)
Psychogenic	207 (19.6)
ED duration (n [%])	
< 1 year	274 (26.1)
≥ 1 year	784 (74.1)
IIEF-EF domain score at baseline (mean ± SD)	14.8 ± 6.2
SEP 2 at baseline	47.8
SEP 3 at baseline	21.2

Patients' baseline characteristics are reported in Table 2. The mean age was 54.8 years, the average weight was 80.3 kg, with an average height of 172.9 cm, and 99.9% were Caucasian. Approximately 74% of patients had an ED history of 1 year or more and the baseline ED severity was classified as moderate or severe in 58.2% of the patients. The ED etiology was clinically determined by investigators and reported as organic in 34.6%, mixed in 45.8% and psychogenic in 19.6% of patients.

Approximately one-quarter of the patients were smokers and 40.7% of the patients consumed alcohol.

The mean number of doses per week in the three times per week and the on-demand regimen was 2.33 and 1.89, respectively ($P < 0.001$)

3.2 Primary endpoint analysis: preference by TPQ

Of the 1 058 subjects who answered the TPQ, 561 (59.1%) chose the on-demand treatment regimen and 389 (40.9%), chose the three times per week regimen. This same pattern of patient choice was observed regardless of whether patients were randomly assigned to the three times per week subgroup A (dosing Monday, Wednesday and Friday) or B (dosing Tuesday, Thursday and Saturday), and regardless of the sequence of cross-over treatment schedules (on-demand followed by three times per week or the reverse). Furthermore, the analysis of preference based on baseline characteristics showed that preference was not dependent on the patients' age or the etiology, severity and duration of ED.

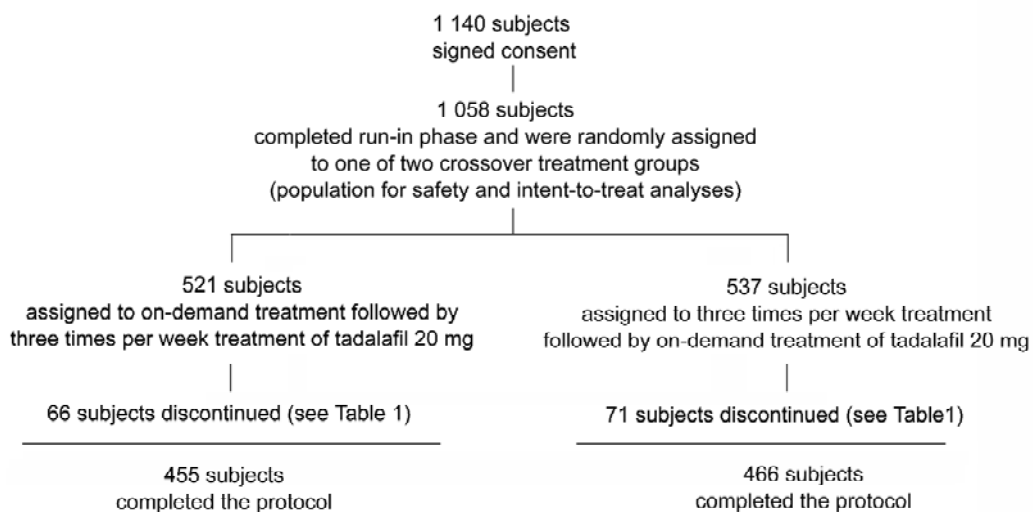


Figure 2. Patient disposition.

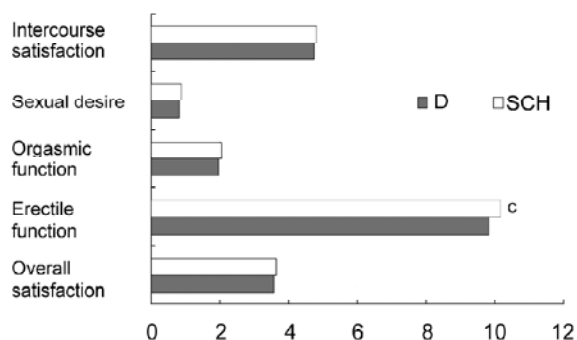


Figure 3. Summary of secondary efficacy variables. International Index of Erectile Function (IIEF) domains: variations from baseline to endpoint. Score range of the IIEF domains: intercourse satisfaction, 0-15; sexual desire, 2-10; orgasmic function, 0-10; erectile function, 1-30; overall satisfaction, 2-10. *P* values are from a cross-over analysis of variance model that includes treatment regimen, pooled site, patient, baseline value and period. The model additionally includes baseline-value-by-treatment-regimen interaction if the latter is significant at *P* < 0.10. ^c*P* < 0.01, compared with D. D, on-demand regimen; SCH, three times per week regimen; IIEF, International Index of Erectile Function.

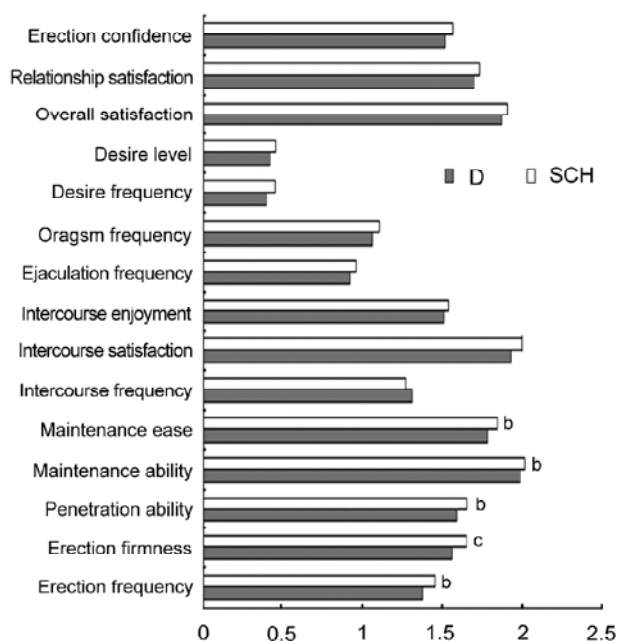


Figure 4. Summary of secondary efficacy variables. IIEF items: Variations from baseline to endpoint. *P* values are from a cross-over analysis of variance model that includes treatment regimen, pooled site, patient, baseline value, and period. The model additionally includes baseline-value-by-treatment-regimen interaction if the latter is significant at *P* < 0.10. *P*-values are for the comparison of on-demand (D) versus three times per week (SCH) regimens. ^b*P* < 0.05, ^c*P* < 0.01, compared with D. D, on-demand regimen; SCH, three times per week regimen; IIEF, International Index of Erectile Function.

3.3 Secondary endpoint analyses: IIEF and SEP

The overall mean IIEF score significantly improved compared to the baseline for both treatment regimens. A sub-analysis of the IIEF domains showed similar improvements for both regimens in all but in the Erectile Function (IIEF-EF) domain, which improved from 14.80 at the baseline to 24.67 with the on-demand regimen, and to 25.00 with the three times per week regimen (*P* = 0.012) (Figure 3). The analysis of the single items of IIEF showed that patients in the three times per week regimen scored significantly better in the questions on intercourse satisfaction (*P* = 0.012), maintenance ease (*P* = 0.026), penetration ability (*P* = 0.034), erection firmness (*P* = 0.006) and erection frequency (*P* = 0.034), whereas no difference was reported in the remaining questions (Figure 4).

Stratifying patients for baseline severity of ED showed a higher efficacy of the on-demand regimen in patients with mild ED, whereas the three times per week regimen was more effective in patients with severe ED (Figure 5).

SEP questionnaire results are shown in Figure 6. In response to the SEP3 question (Did your erection last long enough for you to have successful intercourse?), the mean per patient success rate improved from 19.6% at the baseline to 72.9% at the endpoint for the on-demand regimen, and from 19.0% to 75.9% for the three times per week regimen.

In response to the SEP5 question (Were you satisfied overall with this sexual experience?), the mean per patient rate improved from 6.3% at the baseline to 63.0% at the endpoint for the on-demand regimen and from 6.2% to 66.0% for the three times per week regimen. For all SEP questions the improvement reported with the three times per week regimen was significantly higher

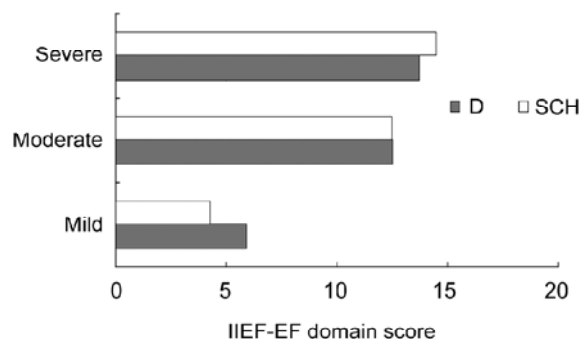


Figure 5. Change from baseline in IIEF-EF domain by baseline severity stratum. D, on-demand regimen; IIEF, International Index of Erectile Function; SCH, three times per week regimen.

Table 3. Summary of treatment emergent adverse events (frequency \geq by decreasing frequency of occurrence. Treatment emergent adverse events (TEAE) are defined as events that first occurred or worsened after baseline. Baseline TEAE were secondary conditions and events recorded before randomization. This table shows TEAE with \geq 1% incidence in any period; these are not additive as a single patient may have reported more than one event. D, on-demand regimen; SCH, three times per week regimen.

TEAE	D		SCH		P value
	n	(%)	n	(%)	
Headache	60	(5.7)	56	(5.3)	0.775
Myalgia	35	(3.3)	45	(4.3)	0.305
Dyspepsia	27	(2.6)	30	(2.8)	0.789
Abdominal pain upper	20	(1.9)	31	(2.9)	0.156
Flushing	18	(1.7)	27	(2.6)	0.228
Back pain	14	(1.1)	10	(0.9)	0.539
Gastritis	12	(1.1)	23	(2.2)	0.087

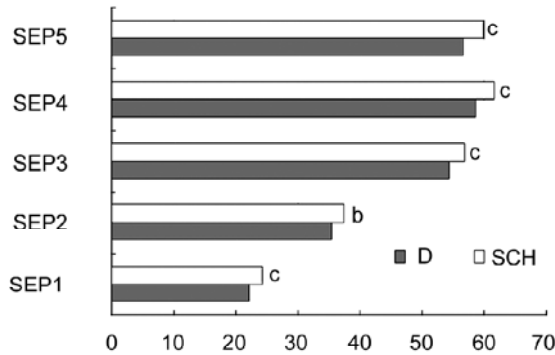


Figure 6. Sexual encounter variations from baseline to endpoint for two treatment regimens of 20 mg of tadalafil. Mean per-patient percentage of “yes” responses to Sexual Encounter Profile (SEP) questions. SEP1: Were you able to achieve at least some erection (some enlargement of the penis)? SEP2: Were you able to insert your penis into your partner’s vagina? SEP3: Did your erection last long enough for you to have successful intercourse? SEP4: Were you satisfied with the hardness of your erection? SEP5: Were you satisfied overall with this sexual experience? For each variable, population summarized consists of those patients having both baseline and at least one postbaseline data. Mean within treatment regimen of change from baseline to endpoint. P values are from a cross-over analysis of variance model that includes treatment regimen, pooled site, patient, baseline value, and period. The model additionally includes baseline-value-by-treatment-regimen interaction if the latter is significant at $P < 0.10$. ^b $P < 0.05$, ^c $P < 0.01$, compared with D. D, on-demand regimen; SCH, three times per week regimen; IIEF, International Index of Erectile Function.

than that with the on-demand regimen.

3.4 Adverse events

Both treatment regimens were well tolerated and no

deaths were reported. Adverse events were rare and generally mild and caused early discontinuation in 4.6% of patients (Table 1). No significant difference in the incidence of adverse was found comparing the two treatment regimens (Table 3).

4 Discussion

The aim in the treatment of ED is to restore an erection satisfaction for the needs of the patient. The PDE5 inhibitors are currently the first therapeutic line in ED treatment, and all the three available agents, sildenafil, vardenafil and tadalafil, are effective and safe [4–6]. Actually, there are no data supporting superiority for any one of them in terms of efficacy or safety, and both clinician and patient make their choice considering several factors related to the sexual activity and the preference of the patient and to the peculiar pharmacokinetic characteristics of these drugs (e.g. the possible interference with alcohol and food and the duration of clinical effects).

As patient’s reported outcome is the gold-standard in efficacy evaluation, it is currently widely accepted that patient’s preference should be regarded as the leading criterion in the treatment strategy [7, 8]. Several preference studies comparing PDE5 inhibitors have been conducted, but for most of them the interpretation of the results is affected by important design flaws, including absence of randomization, non-equivalence of the doses used for the compared drugs, questionable data analysis, and period and carryover effects [9]. The SURE study was a randomized, cross-over trial where two regimens

of the same drug were compared [3]. This study design is the best choice for comparative studies, and adds reliability to both the preference and efficacy results obtained.

The SURE study enrolled 4 262 patients in 14 European countries, and showed that tadalafil was equally effective and well tolerated in both treatment regimens, and that an unexpectedly high number of patients (42.2%) preferred the novel three times per week treatment [3]. However, efficacy results showed a slightly higher improvement in all SEP questions and in all but one IIEF domains with the three times per week compared to the on-demand regimen. Although statistically significant, these differences were not considered clinically significant by the authors because of the small numerical improvement of the scores and the large sample size.

The present analysis of the Italian data subset confirms that both regimens provide excellent efficacy and tolerability, and that in the clinical practice the patient could choose between the two alternative but equally effective treatments according to his personal needs and preference. However, the finding of a statistically higher improvement in all SEP questions and in the IIEF-EF domain score with the three times per week compared to the on-demand regimen is also confirmed in the present subsample, which is smaller and geographically more homogeneous than the whole SURE study dataset. Furthermore, when patients were stratified for severity of ED, a superiority of the three times per week regimen in improving the IIEF-EF domain score was shown in severe patients, whereas the on-demand regimen was more effective in mild patients. However, this difference was numerically small and hardly perceivable by patients. This is confirmed by the preference data analysis, showing that the baseline severity of ED could not predict the preference pattern.

Although not big enough to be considered clinically important, the statistically higher efficacy of the three times per week regimen is meaningful from a speculative viewpoint. It has recently been supposed that the assumption of PDE5 inhibitors on a regular base, providing at steady serum levels and a higher drug exposure, might improve the endothelial function of the corpus cavernosum, therefore enhancing erectile function beyond that observed with the on-demand treatment [10]. In our study the mean number of doses per week assumed by patients was 2.33 and 1.89 in the three times per week and the on-demand regimen, respectively ($P < 0.001$).

Although this has not translated in a clinically higher efficacy of the three times per week regimen in the overall population in study, a wider, perhaps clinically significant difference is evident in the subgroup of patients with severe ED. It could be hypothesized, then, that severe patient can benefit more than mild patients from the higher exposure to tadalafil reported in the three times per week regimen. This observation would support a rehabilitative role of tadalafil three times per week in severe ED and could open new interesting therapeutic perspectives for the PDE5 inhibitors in the treatment of ED.

In conclusion, the analysis of the Italian dataset of the SURE study confirms that tadalafil is effective and well tolerated whether used as a traditional on-demand treatment or in a novel three times per week regimen. In the decision-making process that, through interaction between clinician's guide and patient's preference, leads to the selection of the optimal treatment of ED, these observations provide a scenario where not only the drug but also the treatment regimen can be chosen, further increasing our ability to tailor treatment to an individual patient's needs.

Acknowledgment

Christine Kuepfer, Sabine Weitckus, Lucio Varanese, (Eli Lilly), Flavia Fascetti, Lapo Feri, Pierluigi Crisà (Eli Lilly Italy) provided assistance with the study and in the preparation of this manuscript.

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