

Efficacy and Safety of Tadalafil in Men With Erectile Dysfunction Following Spinal Cord Injury

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Objective: To determine the efficacy and safety of tadalafil when taken on demand by men with erectile dysfunction (ED) secondary to traumatic spinal cord injury (SCI).

Design and Setting: Multicenter, randomized, double-blind, placebo-controlled, flexible dose-titration, parallel-group study in clinical practices in Europe.

Patients: Enrolled patients had ED secondary to SCI (all spinal levels) and sustained 6 months or longer before visit 1.

Interventions: After a 4-week run-in period, patients were randomly assigned to tadalafil, 10 mg, (n=142) or placebo (n=44) for a 12-week, on-demand treatment period with assessments at 4-week intervals. The dose of tadalafil was maintained or titrated (10 or 20 mg) at 4 and 8 weeks.

Main Outcome Measures: Efficacy was measured using the International Index of Erectile Function (IIEF), Sexual Encounter Profile (SEP), and Global Assessment Question (GAQ). Treatment-emergent adverse events and vital signs were collected at each visit.

Results: Mean age was 38 years. Mean baseline IIEF erectile function domain score was 13.4, and following 12 weeks of treatment, 22.6 for tadalafil and 13.6 for placebo ($P < .001$). After treatment, the tadalafil group compared with the placebo group was significantly greater ($P < .001$) in mean per-patient percentage of successful penetration attempts (SEP question 2; 75.4% vs 41.1%) and intercourse attempts (SEP question 3; 47.6% vs 16.8%); percentage of improved erections (GAQ question 1; 84.6% vs 19.5%); and ejaculatory frequency (IIEF question 9; $P = .03$). The 2 most common treatment-emergent adverse events in the tadalafil group compared with placebo were headache (8.5% vs 4.5%) and urinary tract infection (7.7% vs 6.8%).

Conclusions: Tadalafil (10 mg and 20 mg) improved erectile function and was well tolerated by men with ED secondary to traumatic SCI.

Trial Registration: clinicaltrials.gov Identifier: NCT00421083.

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THROUGHOUT THE WORLD, SPINAL cord injury (SCI) occurs most often in young men, resulting in negative physical, social, and psychological consequences.¹⁻³ Erectile dysfunction (ED), defined as the inability to attain and maintain penile erection sufficient for



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satisfactory sexual performance,⁴ is a common complication in men with SCI. The degree of sexual impairment can vary depending on the extent and level of the neurological lesion. Only 25% of men with SCI have erections adequate for intercourse.⁵ A current treatment option for patients with ED and SCI is an oral phosphodiesterase 5 (PDE5) inhibitor, which is a first-line treatment for most men with ED.

Following sexual stimulation, a PDE5 inhibitor facilitates an erection through the second messenger cyclic guanosine monophosphate (cGMP) in smooth muscle cells (**Figure 1**).⁶ Tadalafil is a potent inhibitor of PDE5 that has been shown to be efficacious and well tolerated in men with ED.⁷ Additional studies with tadalafil indicate that it could be an important treatment option for ED in men with SCI.^{8,9} This study was conducted to determine the efficacy and safety of tadalafil in men with ED subsequent to traumatic SCI.

METHODS

STUDY DESIGN

This randomized, double-blind, placebo-controlled, parallel group, flexible dose-titration study was conducted in France, Germany, Italy, and Spain to determine the efficacy

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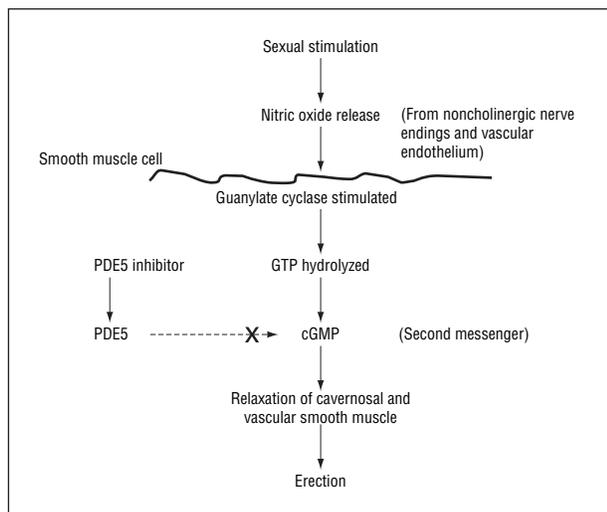


Figure 1. Mechanism of phosphodiesterase 5 (PDE5) inhibitors. Appropriate sexual stimuli evoke penile erection by a series of complex biological reactions that result in penile tumescence and rigidity. This mechanism is mediated by nitric oxide. Levels of the second messenger cyclic guanosine monophosphate (cGMP) are regulated by PDE5. PDE5 inhibitors act on PDE5 to inhibit metabolism of cGMP, resulting in increased intracellular concentrations of cGMP, enhanced relaxation of cavernosal and vascular smooth muscle cells, and penile erection. GTP indicates guanosine triphosphate. Reprinted with permission from Eardley and Cartledge.⁶

and safety of tadalafil when taken on demand (a maximum of 1 dose per day before sexual activity) by men with ED following a traumatic SCI.

This study consisted of 2 periods: a treatment-free run-in period of 4 weeks followed by a 12-week treatment period (**Figure 2**). Patients who signed informed consent at visit 1 (V1) were instructed to make at least 4 sexual intercourse attempts without medication during the run-in period. After the run-in period (V2), eligible patients were randomly assigned (3:1) to tadalafil, 10 mg, or placebo to begin the 12-week treatment period with assessments after each 4-week interval. After the first treatment interval (V3), tadalafil 10 mg was titrated to tadalafil 20 mg (2 10-mg tablets of tadalafil) or unchanged. After the second treatment interval (V4), the dose of tadalafil was titrated to tadalafil 20 mg, tadalafil 10 mg, or unchanged. The investigator determined whether to titrate based on the patient's response to the drug during the previous treatment interval. Subjects were instructed to take 1 dose of study drug with water before the potential for sexual activity, regardless of food. Patients could initiate sexual activity at various times after dosing to determine their own optimal windows of opportunity. They were instructed to take no more than 1 dose per day.

Random assignment (3:1) of patients to a treatment group was stratified by degree of Residual Erectile Function (REF); severity of SCI, as defined by the American Spinal Injury Association (ASIA) severity scale¹⁰; and country.

PATIENT POPULATION

Enrolled patients included men who were at least 18 years old with ED that was subsequent to traumatic SCI of any spinal level and neurological impairment (all levels of severity except normal as determined by the ASIA scale) and that occurred at least 6 months before V1. Patients agreed not to use any other ED treatment during the run-in or treatment phase and for 96 hours after the final study visit. Key exclusion criteria were men with the following conditions: (1) ED due to untreated endocrine disease or premature ejaculation; (2) radi-

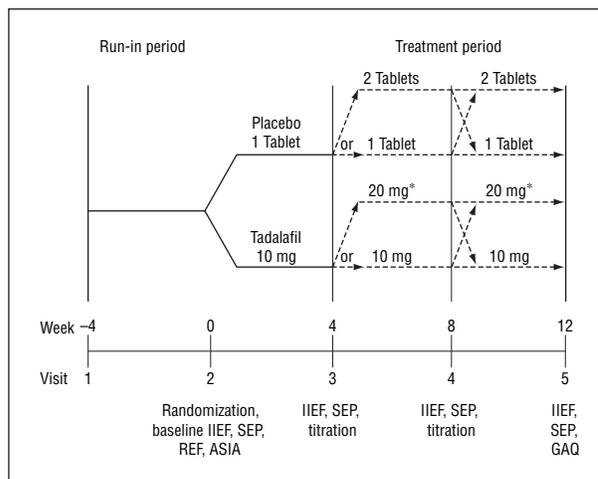


Figure 2. Study design. Asterisk indicates that 20 mg was 2 10-mg tablets of tadalafil. IIEF indicates International Index of Erectile Function; SEP, Sexual Encounter Profile; REF, Residual Erectile Function scale; ASIA, American Spinal Injury Association scale; and GAQ, Global Assessment Questionnaire.

cal prostatectomy who failed to achieve an erection or who had penile implants or clinically significant penile deformities; (3) uncontrolled diabetes mellitus (hemoglobin A_{1c} level higher than 13.0%); (4) clinically significant renal or hepatobiliary disease; (5) severe or unstable coronary artery disease or cardiac dysfunction, coronary intervention, or any uncontrolled supraventricular arrhythmia; (6) hypertension (>170 mm Hg systolic or >100 mm Hg diastolic) or hypotension (<90 mm Hg systolic or <50 mm Hg diastolic); (7) recent central nervous system injury; (8) current treatment with nitrates, cancer chemotherapy, antiandrogens, or α -blockers; (9) previous use of tadalafil; (10) prior ineffective treatment with PDE5 inhibitors in the opinion of the investigator; and (11) any condition that would interfere with the subject's ability to provide informed consent or comply with study instructions, would place the subject at increased risk, or might confound interpretation of the study results. Patients who had experienced autonomic dysreflexia in the past were not excluded from participating in this study. Nevertheless, if sexual activity was regarded by the investigator as inadvisable for a given patient because of an increased risk of severe autonomic dysreflexia, that patient could be excluded according to the last exclusion criterion stated here. Patients agreed not to use any other ED treatments for at least 4 weeks before receiving the initial dose of study drug (ie, during the run-in period), during the treatment phase of the study, and for 96 hours after the final study visit was completed. Patients started study drug treatment after randomization at V2.

MEASURES OF EFFICACY

Primary measures of efficacy were the International Index of Erectile Function (IIEF) erectile function (EF) domain and Sexual Encounter Profile diary questions 2 (SEP2) and 3 (SEP3).

The IIEF is a validated, multidimensional, self-administered questionnaire used to assess the efficacy of ED therapy.¹¹ The IIEF consists of 15 questions that are grouped into 5 domains. The IIEF questionnaire was administered at the end of the run-in period (baseline) and at each visit during the 12 weeks of treatment. The EF domain consists of 6 questions with a possible score of 1 to 30. The EF domain is a validated diagnostic tool for classifying ED severity.¹² Severity of ED was defined using the IIEF-EF domain score: 5 or lower, no attempts at intercourse; 6 to 10, severe ED; 11 to 16, moderate ED; 17 to 21,

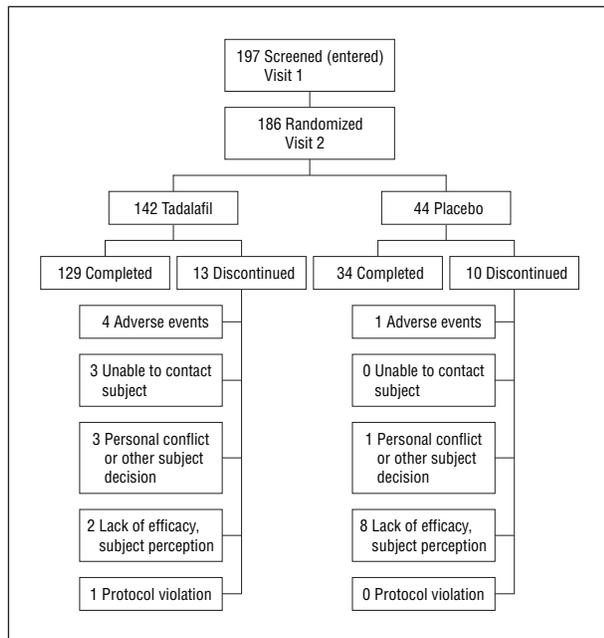


Figure 3. Patient disposition.

mild to moderate ED; 22 to 25, mild ED; and 26 or higher, “normal” erectile function. An increase of 4 to 5 in the IIEF-EF score is considered to be clinically significant.

The SEP diary is another common measure of efficacy of ED therapy and consists of 5 questions. The questions address the sexual events the patient experienced when attempting intercourse. The SEP2 asked, “Were you able to insert your penis into your partner’s vagina?” and the SEP3 asked, “Did your erection last long enough for you to have successful intercourse?” In this study, the questionnaire was administered at each visit of the treatment phase and answered by patients after each sexual intercourse attempt during a treatment interval.

Secondary measures of efficacy in this study included Global Assessment Question 1 (GAQ1) and GAQ2. These questions were presented to patients at the last visit of the study and asked whether treatment improved their erections (GAQ1) and, if so, whether treatment improved their ability to engage in sexual activity (GAQ2). Additional secondary measures of efficacy were the other 4 IIEF domains (intercourse satisfaction, orgasmic function, sexual desire, overall satisfaction), IIEF question 9 (ejaculation frequency), and IIEF question 10 (orgasm frequency). Another point of interest in this study, although not a measure of efficacy, was the percentage of patients with normal IIEF-EF domain scores (≥ 26) at the end of the study.

ANALYSIS OF SAFETY

Safety was assessed by evaluating all reported treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), and vital signs (blood pressure and heart rate) at each visit of the 12-week treatment phase. Vital signs were also collected before the start of the run-in phase. All events were coded to Medical Dictionary for Regulatory Activities (MedDRA) version 8.0 (<http://www.meddrasso.com/MSSOWeb/index.htm>).

STATISTICAL ANALYSIS

A sample size of 180 was used to provide at least 90% power to detect significant treatment effects for the tadalafil 10-mg dose on each of the 3 end points at an α level of .05. There was no α adjustment for the 3 primary efficacy measures (IIEF-EF do-

main, subject SEP2, and subject SEP3) because all 3 variables were required to reach statistical significance for the null hypothesis to be rejected. The sample size was driven by the SEP2 analysis in the entire subject population because this test required the most subjects to detect a significant difference.

Primary and secondary efficacy analyses were conducted on an intent-to-treat basis. Primary efficacy analyses were performed on original scale data using change from baseline. No data transformations were performed. The 2 treatment groups, tadalafil and placebo, were compared throughout the study. For each efficacy variable, the analysis population included all patients with a baseline measurement and at least 1 postbaseline measurement.

We analyzed IIEF-EF domain scores using a last-observation-carried-forward convention. For each SEP question, baseline and postbaseline scores were percentage of yes responses relative to number of sexual encounters during the run-in period and the treatment period, respectively. Postbaseline SEP questions included percentage of yes responses relative to number of sexual attempts in the treatment period. Proportions of yes responses to SEP diary questions were treated as continuous variables. We analyzed IIEF-EF domain, SEP2, and SEP3 using an analysis of covariance (ANCOVA) model that included terms of treatment group, pooled site, baseline value for each primary efficacy variable, severity of SCI, and degree of REF at baseline. A term for the interaction of the treatment with baseline value was included if the interaction was significant at $P < .10$. The IIEF intercourse satisfaction, orgasmic function, sexual desire, and overall satisfaction domains and the individual IIEF questions were analyzed by similar ANCOVA models.

Secondary analysis to evaluate GAQ at end point by treatment group was performed using a logistic regression model including terms of pooled site, treatment group, erectile function at baseline, and severity of SCI. Only patients who responded to the GAQ were included in the analysis. The percentage of patients who attained an IIEF-EF domain score of 26 to 30 at end point was analyzed using a logistic model that included terms of pooled site, treatment group, degree of REF at baseline, baseline IIEF-EF domain, and baseline \times treatment interaction (if $P < .10$).

RESULTS

This multicenter study included 197 patients who signed informed consent forms (Figure 3). Of these patients, 186 were randomly assigned in a 3:1 ratio to tadalafil ($n=142$) or placebo ($n=44$). In the tadalafil treatment group, 129 patients (91%) completed the study. Treatment was discontinued by 4 patients (2.8%) because of adverse events and by 2 patients (1.4%) because of lack of efficacy. In the placebo group, 34 patients (77%) completed the study. Eight patients (18.2%) discontinued treatment because of lack of efficacy and 1 (2.3%) because of adverse events.

The demographic characteristics of patients at baseline were comparable between treatment groups (Table 1). The mean age was 38 years (range, 18-66 years). Nearly 70% of the patients in each group had ASIA impairment grade A (complete lesion), and at least 60% in each treatment group had SCI at T11 or above. The mean baseline IIEF-EF domain score was 13.4, and more than 60% of patients had moderate to severe ED at baseline based on their IIEF-EF domain score (moderate, 11-16; severe, 1-10). The largest percentage of patients in

Table 1. Patient Baseline Characteristics^a

Characteristic	Tadalafil (n = 142)	Placebo (n = 44)	Total (N = 186) ^b
Mean age, y	37	39	38
ED etiology			
Mixed	13 (9.2)	4 (9.1)	17 (9.1)
Organic	129 (90.8)	40 (90.9)	169 (90.9)
ED severity (score) ^{12c}			
Mild (17-30)	46 (32.9)	11 (25.0)	57 (31.0)
Moderate (11-16)	42 (30.0)	16 (36.4)	58 (31.5)
Severe (1-10)	52 (37.1)	17 (38.6)	69 (37.5)
ED duration			
≥1 y	131 (92.3)	40 (90.9)	171 (91.9)
≥6 mo to <1 y	9 (6.3)	4 (9.1)	13 (7.0)
≥3 mo to <6 mo	2 (1.4)	0	2 (1.1)
Prior ED treatment			
Sildenafil citrate	74 (52.1)	22 (50.0)	96 (51.6)
Vardenafil hydrochloride	16 (11.3)	4 (9.1)	20 (10.8)
Other	25 (17.6)	6 (13.6)	31 (16.7)
None	27 (19.0)	12 (27.3)	39 (21.0)
REF grade			
No tumescence (0)	12 (8.5)	2 (4.5)	14 (7.5)
Some tumescence, no rigidity (1)	25 (17.6)	8 (18.2)	33 (17.7)
Normal tumescence, weakened rigidity (2)	37 (26.1)	14 (31.8)	51 (27.4)
Normal tumescence, slightly weakened rigidity (3)	59 (41.5)	20 (45.5)	79 (42.5)
Normal tumescence and rigidity (4)	9 (6.3)	0	9 (4.8)
ASIA impairment grade			
Complete lesion (A)	99 (69.7)	30 (68.2)	129 (69.4)
Incomplete lesion (B)	17 (12.0)	6 (13.6)	23 (12.4)
Incomplete lesion (C)	8 (5.6)	6 (13.6)	14 (7.5)
Incomplete lesion (D)	18 (12.7)	2 (4.5)	20 (10.8)
Injury level			
Cervical (C1-C7)	23 (16.8)	5 (11.9)	28 (15.6)
Thoracic (C8-T11)	82 (59.9)	29 (69.0)	111 (62.0)
Lumbosacral (T12-S5)	32 (23.4)	8 (19.0)	40 (22.3)

Abbreviations: ASIA, American Spinal Injury Association; ED, erectile dysfunction; REF, Residual Erectile Function.

^aUnless otherwise noted, values are given as number (percentage).

^bPatients with available data.

^cPatients were included based on a history of erectile dysfunction. Subsequent assessment of erectile function by the International Index of Erectile Function (IIEF) at baseline revealed that 6 study participants (3.2%) had an erectile function domain score in the normal range (26-30).

each treatment group had REF grade 2 (normal tumescence, weakened rigidity) (27.4%) or grade 3 (normal tumescence, slightly weakened rigidity) (42.5%).

Prior to entering the study, 96 patients (51.6%) were taking sildenafil citrate and 20 patients (10.8%) were taking vardenafil hydrochloride. Treatments for ED other than a PDE5 inhibitor were used by 31 patients (16.7%), and 39 patients (21.0%) were taking no treatment.

PRIMARY EFFICACY

Tadalafil significantly improved erectile function compared with placebo ($P < .001$) as measured by improvement in the IIEF-EF domain score and in SEP2 and SEP3 responses (**Figure 4**). At baseline, the mean IIEF-EF domain score was 13.5 for tadalafil and 13.0 for placebo compared with 22.6 for the tadalafil group and 13.6 for placebo after 12 weeks of treatment ($P < .001$). In response to SEP2, mean per-patient percentage of attempts with successful penetration was 75.4% for tadalafil and 41.1% for placebo ($P < .001$). In response to SEP3, the mean per-patient percentage of successful sexual intercourse at-

tempts was 47.6% for tadalafil and 16.8% for placebo ($P < .001$).

SECONDARY EFFICACY

In addition to the EF domain of IIEF, the other 4 domains were evaluated (intercourse satisfaction, orgasmic function, sexual desire, and overall satisfaction). Compared with placebo, the change from baseline to end point in the tadalafil group was statistically significant ($P < .01$) in all IIEF domains except the desire domain ($P = .97$). There was also a significant improvement in ejaculation frequency (IIEF question 9) ($P = .03$) and orgasm frequency (IIEF question 10) ($P = .01$).

An IIEF-EF domain score lower than 26, indicating ED, was assessed at baseline for 137 of 142 patients in the tadalafil treatment group (96.5%) and for 43 of 44 patients in the placebo group (97.7%). Seventy-four patients (54.0%) with scores lower than 26 in the tadalafil group and 5 patients (11.6%) in the placebo group achieved a normal score (≥ 26) after 12 weeks of treatment on demand (**Figure 5**). This difference between

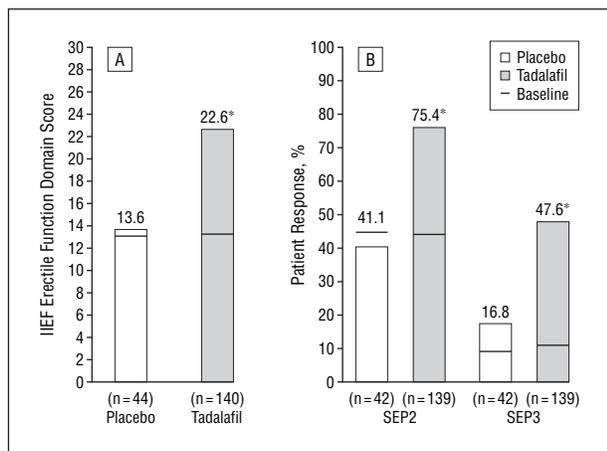


Figure 4. Primary measures of efficacy. A, International Index of Erectile Function (IIEF) erectile function domain scores at baseline and after 12 weeks of treatment. The score is the sum of the scores from IIEF questions 1 through 5 and 15. Asterisk indicates $P < .001$ between treatment groups after 12 weeks of treatment. B, Patient responses to Sexual Encounter Profile diary question 2 (SEP2) and SEP3. Percentages are mean per-patient percentages of yes responses to SEP2 (“Were you able to insert your penis into your partner’s vagina?”) or SEP3 (“Did your erection last long enough for you to have successful intercourse?”).

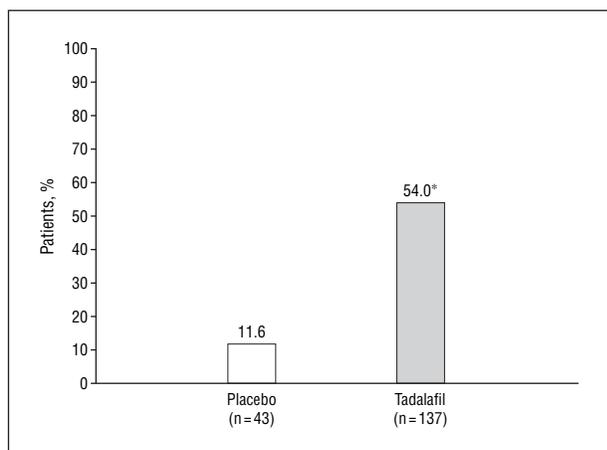


Figure 5. International Index of Erectile Function (IIEF) erectile function domain (EF) score 26 or higher after 12 weeks of treatment. Of the 142 patients randomly assigned to tadalafil, 137 (96.5%) had an impaired IIEF-EF score at baseline (< 26). Of the 44 patients randomly assigned to placebo, 43 (97.7%) had an impaired IIEF-EF score at baseline. Of the patients with an impaired IIEF-EF score, 74 (54.0%) in the tadalafil group and 5 (11.6%) in the placebo group achieved a normal score after 12 weeks of treatment. Asterisk indicates $P < .001$ between treatment groups after 12 weeks of treatment.

the tadalafil and placebo groups was statistically significant ($P < .001$). Further analysis of IIEF-EF domain scores showed that for a subgroup of patients who had severe ED at baseline (IIEF-EF domain score ≤ 10), a larger percentage in the tadalafil group (40%) achieved an IIEF-EF domain score of 26 or higher after treatment compared with placebo (0%) ($P < .001$).

In the tadalafil group, the IIEF-EF domain score improved from baseline to end point for all baseline ED severity categories with the greatest changes occurring in the moderate and severe categories. When compared with placebo, these changes were statistically significant (**Figure 6**).

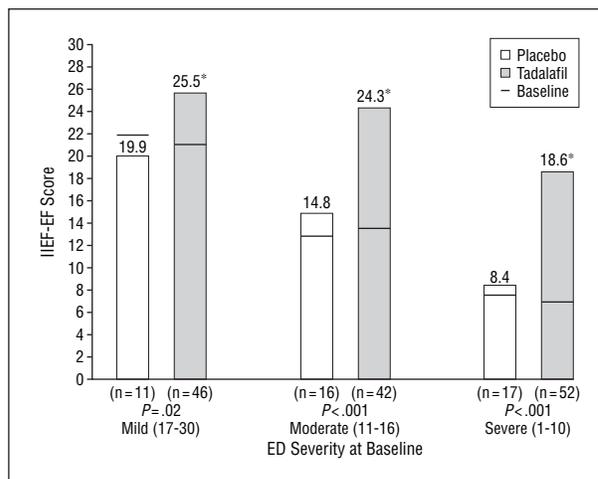


Figure 6. International Index of Erectile Function (IIEF) erectile function domain (EF) score after 12 weeks of treatment by erectile dysfunction (ED) severity. Patients were grouped by ED severity at baseline and then their mean IIEF-EF scores at baseline and end point were determined. P values compare the mean IIEF-EF score at end point of the tadalafil treatment group vs end point score for the placebo. Asterisk indicates statistical significance compared with placebo.

The percentage of yes responses to GAQ1 (“Did the treatment improve your erections?”) was 84.6% for the tadalafil group compared with 19.5% for placebo ($P < .001$). For GAQ2 (“Did the treatment improve your ability to engage in sexual activity?”), 78.5% of patients in the tadalafil group said yes compared with 14.6% for placebo ($P < .001$) (**Figure 7**).

The 3 primary efficacy variables, IIEF-EF domain score, SEP2, and SEP3, were further analyzed based on degree of REF (grade 1 and grades 2-4), ASIA score (grade A and grades B-D), and neurological injury level (C1-T11 and T12-S5) (**Table 2** and **Table 3**). Overall, the statistically significant improvement in the efficacy variables observed in the tadalafil group applied to patients with different severities of baseline REF, patients with complete lesions (no remaining motor or sensory function), and patients with incomplete lesions and less severe SCI. Analyses based on neurological injury level (C1-T11 and T12-S5) showed that tadalafil was again superior to placebo regardless of the level of SCI.

SAFETY

Patients in the tadalafil group received a mean (SD) of 26.6 (17.3) doses over 94.6 (16.8) days compared with 18.4 (12.9) doses over 87.9 (19.4) days for placebo. In total, 101 of 142 patients (71%) randomly assigned to the tadalafil group were exposed to tadalafil 20 mg. In the last treatment interval, 91 of 142 patients (64%) received tadalafil 20 mg.

Tadalafil was safe and well tolerated with few TEAEs (**Table 4**). Fifty patients in the tadalafil group (35%) and 15 in the placebo group (34%) reported at least 1 TEAE. The most frequently reported TEAE in the tadalafil group was headache for 12 of 142 patients (8.5%). Other TEAEs reported by 2% or more of the patients in the tadalafil group were urinary tract infection (7.7%), upper abdominal pain (2.1%), and muscle spasticity

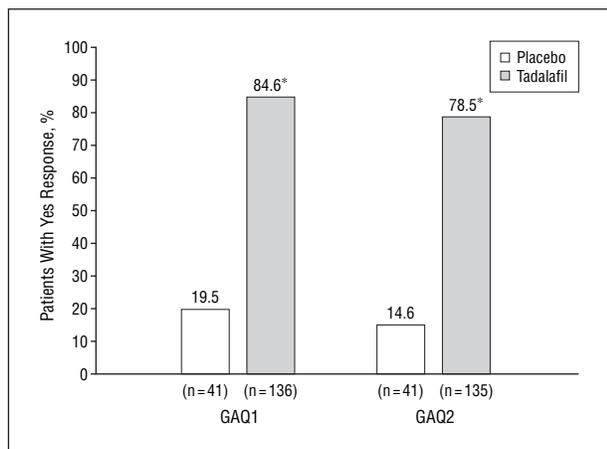


Figure 7. Responses to Global Assessment Question 1 (GAQ1) and GAQ2. Asterisk indicates $P < .001$ between treatment groups for GAQ1 ("Has the treatment you have been taking during this study improved your erections?") and GAQ2 ("If yes to GAQ1, has the treatment improved your ability to engage in sexual activity?").

(2.1%). There were no cases of back pain, dyspepsia, or autonomic dysreflexia. Most TEAEs reported by patients in the tadalafil group were mild (50%) or moderate (38%) in severity, which was similar to placebo (60% mild, 33% moderate) (**Table 5**).

A similar percentage of patients in the 2 groups (4% tadalafil, 5% placebo) reported an SAE, and, in the opinion of the investigator, none of the SAEs were related to study drug. The percentage of patients who discontinued the study because of an adverse event was similar in both groups (3% tadalafil, 2% placebo). No deaths occurred in this study. No clinically relevant changes in pulse rate or in systolic or diastolic blood pressure occurred at any visit.

COMMENT

The current incidence of SCI worldwide is between 10.4 and 83 per million inhabitants per year.¹ Reports in the literature consistently show that SCI occurs most often in young men (mean age, 33 years vs 57 years in the general male population) and has negative consequences, including the inability to engage in sexual activity.^{1-3,13}

After traumatic SCI, 3 types of erections have been described: reflexogenic, psychogenic, and mixed (reflexogenic and psychogenic).¹⁴ Reflexogenic erections are involuntary and require intact S2 to S4 neural pathways. Psychogenic erections are elicited by supraspinal stimuli. Mixed erections may occur when the spinal cord lesion is below L2 and above S2. In general, the ability to achieve and maintain an erection is greater with an incomplete higher-level SCI.

To our knowledge, our study is the first (and a unique) randomized, double-blind, placebo-controlled, parallel-group study to assess the efficacy and safety of tadalafil in patients with ED caused by SCI. Del Popolo's group⁸ reported data from a crossover study comparing tadalafil with sildenafil in a small cohort (n=28 completers) of SCI patients with ED. On the other hand, data reported by Goetz and coworkers⁹ were based on an open-label exploratory study to assess the efficacy and safety

Table 2. Grades for the Residual Erectile Function and American Spinal Injury Association Scales

Scale Grade	Description
Residual Erectile Function scale (REF)	
Grade 0	No tumescence, no rigidity
Grade 1	Some tumescence, no rigidity
Grade 2	Normal tumescence, weakened rigidity
Grade 3	Normal tumescence, slightly weakened rigidity
Grade 4	Normal tumescence, normal rigidity
American Spinal Injury Association scale (ASIA)	
Grade A	Complete: no motor or sensory function is preserved in the sacral segments
Grade B	Incomplete: sensory but not motor function is preserved below the neurological injury level and includes the sacral segments S4-S5
Grade C	Incomplete: motor function is preserved below the neurological injury level, and more than half of key muscles below the neurological injury have a muscle grade less than 3
Grade D	Incomplete: motor function is preserved below the neurological injury level, and at least half of key muscles below the neurological injury have a muscle grade of 3 or more
Grade E	Normal: motor and sensory functions are normal

of tadalafil in a small cohort of 49 patients with SCI and ED. The present study reports the first robust and objective information regarding the efficacy of tadalafil in SCI patients.

In the present study, tadalafil was administered on demand and significantly improved erectile function, compared with placebo, in men who developed ED following a traumatic SCI. Erectile function was assessed with commonly used efficacy measures of ED (IIEF-EF domain score, SEP2, and SEP3).

In this young population of patients (mean age, 38 years), most had a history of ED of 1 year or longer (91.9%), moderate to severe ED (69.0%), organic ED etiology (90.9%), grade A SCI impairment (69.7%), and a neurological injury level at or above T11 (77.7%). Even with these serious baseline conditions, all 3 primary efficacy variables improved significantly in the tadalafil treatment group compared with placebo ($P < .001$) after 12 weeks of on-demand treatment. In addition, the placebo group had a noticeably low efficacy response, indicating that impairment of erectile function was consistent for the patients in this group. Treatment with tadalafil improved ED from moderate at baseline to mild. After 12 weeks of treatment, 54% of patients had a normal IIEF-EF domain score (≥ 26). A large percentage of patients (40%) with severe ED (IIEF-EF domain score ≤ 10) at baseline achieved a normal score. Because of high baseline scores, there was less change from baseline to end point in the IIEF-EF domain score for patients with mild ED (17-30) than for patients with moderate or severe ED. The percentage of patients who were able to pen-

Table 3. Summary of Efficacy Variables IIEF-EF Domain Score, SEP2, and SEP3 Based on REF, ASIA, and Level of Spinal Cord Injury^a

Characteristic	Tadalafil ^b			Placebo		
	IIEF-EF End Point/ Δ /No.	SEP2 End Point/ Δ /No.	SEP3 End Point/ Δ /No.	IIEF-EF End Point/ Δ /No.	SEP2 End Point/ Δ /No.	SEP3 End Point/ Δ /No.
REF						
Grade 1	21.6/12.7/25	62.1/42.8/25	42.9/40.1/25	9.5/1.5/8	14.1/-3.8/8	0/0/8
Grades 2-4	24.1/8.7/105	85.2/30.5/102	53.5/39.5/102	15.2/0.6/34	50.4/-4.1/32	22.0/10.8/32
ASIA						
Grade A	22.0/9.5/98	71.7/33.0/99	44.1/35.3/99	12.6/0.3/30	33.9/-6.1/28	6.4/1.4/28
Grades B-D	24.0/8.0/42	84.5/28.8/40	56.1/40.5/40	15.8/1.4/14	55.4/0.7/14	37.5/22.0/14
Level of injury						
C1-T11	23.2/9.4/103	77.4/30.3/105	47.9/37.6/105	13.7/0.7/34	41.3/-3.5/33	15.6/6.5/33
T12-S5	20.8/8.0/32	68.6/37.9/29	50.2/36.7/29	14.1/0.5/8	45.2/-5.8/8	23.9/16.3/8

Abbreviations: ASIA, American Spinal Injury Association; ED, erectile dysfunction; IIEF-EF International Index of Erectile Function erectile function domain; REF, Residual Erectile Function; SEP2 and SEP3, Sexual Encounter Profile questions 2 and 3.

^aValues represent mean at end point (after 12 weeks of treatment) and mean change (Δ) from baseline.

^bWhen comparing the tadalafil treatment group with placebo, the change from baseline to end point for each efficacy variable was statistically significant ($P < .05$) except for the IIEF-EF domain score at the T12-S5 level of injury ($P = .06$).

Table 4. Treatment-Emergent Adverse Events in the Tadalafil Group With $\geq 2\%$ Incidence

Event	No. (%) ^a	
	Tadalafil (n=142)	Placebo (n=44)
Headache	12 (8.5)	2 (4.5)
Urinary tract infection	11 (7.7)	3 (6.8)
Upper abdominal pain	3 (2.1)	0
Muscle spasticity	3 (2.1)	0

^a $P > .05$ between treatment groups for each treatment-emergent adverse event.

Table 5. Summary of Treatment-Emergent Adverse Events by Severity

Maximum Severity ^a	No. (%)	
	Tadalafil (n=142) ^b	Placebo (n=44) ^c
Mild	25 (17.6)	9 (20.5)
Moderate	19 (13.4)	5 (11.4)
Severe	6 (4.2)	1 (2.3)
Total	50 (35.2)	15 (34.1)

^aTreatment-emergent adverse event are listed by maximum severity within overall system organ class.

^bTadalafil group includes patients who received tadalafil 10 mg or 20 mg.

^cThere was no significant difference in total treatment-emergent adverse events between treatment groups.

trate their partner (SEP2) improved significantly, the percentage experiencing successful intercourse (SEP3) increased nearly 5-fold, and 84% of patients reported improved erections after 12 weeks of treatment. Overall, the results from the 3 primary ED efficacy variables show that tadalafil was efficacious regardless of severity and level of SCI, degree of REF, and severity of ED. Because of the complex mechanisms associated with erectile function, it is difficult to explain the significant improvement in ejaculation and orgasm frequency, which are both as-

sessed by the orgasmic function domain of the IIEF. Perhaps restoration of erectile function facilitates ejaculation, which occurs during orgasm in men without ED.

This study was not designed or powered to compare clinical responses to tadalafil 10 mg vs 20 mg. The sample size was sufficient to give a 90% power to detect a significant treatment effect for the lower dose of tadalafil (10 mg) in each primary efficacy variable. Because of the flexible-dose design, which allowed investigators to increase or decrease the dose at predetermined visits according to the subject's response to treatment during the interval, efficacy and safety outcomes resulted from exposure to both doses for each single patient over the course of the study. Therefore, it is not feasible to accurately match outcomes to each single dose individually.

Tadalafil was safe and well tolerated with a low incidence of TEAEs and SAEs and a low rate of discontinuation due to AE, similar to the placebo. The AE profile of tadalafil in this study had a lower occurrence of events commonly reported by the general ED population while receiving tadalafil, sildenafil, or vardenafil.¹⁵⁻¹⁷ In this study, headache was reported by 9% of the patients in the tadalafil group while flushing, rhinitis, or dizziness was reported by less than 0.8% of patients. There were no cases of back pain or dyspepsia, both of which are common TEAEs in patients taking tadalafil, sildenafil, or vardenafil.¹⁵⁻¹⁷ Urinary tract infections are a common event in patients with SCI and were reported in this study (Table 4).

In separate reports, the PDE5 inhibitors sildenafil and vardenafil improved erections in men with ED subsequent to SCI. In a review of 2 randomized controlled trials and 4 prospective case series that evaluated sildenafil, 75% to 94% of all patients had improved erections and 30% to 72% had successful intercourse attempts.¹⁸ The most commonly reported AEs associated with sildenafil were considered similar to those previously published and included headache ($\leq 17\%$), facial flushing ($\leq 9\%$), nasal congestion ($\leq 5\%$), dyspepsia ($\leq 4\%$), and visual disturbances ($\leq 4\%$). Treatment was discontinued because of AEs in less than 6% of all patients. In a double-blind, placebo-controlled study with vardenafil, erections im-

proved in 80% of patients and the mean per-patient successful intercourse rate (SEP3) was 59%.¹⁹ The safety profile was considered similar to that in previous studies with vardenafil. Adverse events with 2% or greater incidence in the vardenafil group included headache (15%), flushing (6%), nasal congestion (5%), dyspepsia (4%), and dizziness (2%). In each treatment group, 4% of patients reported severe AEs.

In our study, efficacy data with tadalafil were similar to those observed with the other 2 available PDE5 inhibitors, and the safety profile showed a lower incidence of classic PDE5 inhibitor-related AEs. However, because this was not a head-to-head comparative trial, no other conclusions can be made in this respect. Comparative trials would be needed to conclude that one agent is superior to another. Nevertheless, having a similar efficacy and safety profile, tadalafil shows a unique pharmacokinetic and efficacy profile with a half-life of 17.5 hours (4-5 hours for sildenafil and vardenafil), which is consistent with a clinical efficacy extended up to 36 hours; from a pharmacodynamic perspective, tadalafil is also different from the other drugs in that it shows no interaction with food (the other 2 show interactions with fatty food).^{15-17,20,21} This wider period of responsiveness and absence of interaction with food observed with tadalafil may be perceived by many patients and their sexual partners as benefits because they may allow them to have a more natural sexual experience, giving them latitude to choose the best moment to engage in sexual intercourse rather than plan such activity. Hence, tadalafil may be the agent of choice for SCI patients who do not want to plan their sexual activity around medication dosing.

One potential limitation of the present study was that patients with prior inadequate responses to PDE5 inhibitors were excluded. This exclusion criterion was based on both ethical and methodological grounds. On ethical grounds, it is unlikely that an SCI patient whose ED failed to respond to another PDE5 inhibitor would experience a treatment benefit when treated with tadalafil (or allocated to placebo). On methodological grounds, it is known from clinical experience that erectile function is not improved in only a minority ($\geq 25\%$) of patients with ED associated with SCI when treated with a PDE5 inhibitor. Therefore, we consider it unlikely that excluding nonresponders to other PDE5 inhibitors would have so systematically biased (upward) the efficacy findings as to limit their generalizability to other SCI patient populations. In addition, through the exclusion of nonresponders, we tried to limit the risk of a severely unbalanced sample because of inclusion of an excessive proportion of nonresponders, secondary to these 2 logical and even laudable potential attitudes, that also represent a real threat of severe selection bias: nonresponders' enthusiasm to participate in clinical trials investigating ED treatments and physicians' compassionate attitudes toward this population.

CONCLUSIONS

As in other ED studies that include patients who were difficult to treat owing to preexisting conditions (eg, pros-

tatectomy, diabetes mellitus^{22,23}), tadalafil was efficacious for the treatment of ED after a traumatic SCI. On-demand treatment with tadalafil (10 mg or 20 mg) may help improve the sex lives of patients with ED and SCI and their partners.

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