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Original Articles

EFFICACY AND SAFETY OF TADALAFIL FOR THE TREATMENT OF ERECTILE DYSFUNCTION: RESULTS OF INTEGRATED ANALYSES

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ABSTRACT

Purpose: We conducted integrated analyses of the efficacy and safety of tadalafil, a potent, selective phosphodiesterase 5 inhibitor, for the treatment of erectile dysfunction.

Materials and Methods: A total of 1,112 men with a mean age of 59 years (range 22 to 82) and mild to severe erectile dysfunction of various etiologies were randomized to placebo or tadalafil, taken as needed without food or alcohol restrictions, at fixed daily doses of 2.5 mg., 5 mg., 10 mg., or 20 mg. in 5 randomized, double-blind, placebo controlled trials lasting 12 weeks. The 3 co-primary outcomes were changes from baseline in the erectile function domain of the International Index of Erectile Function and the proportion of "yes" responses to questions 2 and 3 of the Sexual Encounter Profile. Additional efficacy instruments included a Global Assessment Question.

Results: Compared with placebo, tadalafil significantly enhanced all efficacy outcomes. Patients receiving 20 mg. tadalafil experienced a significant mean improvement of 7.9 in International Index of Erectile Function erectile function domain score from baseline ($p < 0.001$ versus placebo), 75% of intercourse attempts (Sexual Encounter Profile question 3, a secondary efficacy outcome) were successfully completed ($p < 0.001$ versus placebo) and 81% reported improved erections at end point compared with 35% in the control group ($p < 0.001$). Tadalafil was consistently efficacious across disease severities and etiologies, as well as in patients of all ages. Tadalafil was well tolerated, and headache and dyspepsia were the most frequent adverse events.

Conclusions: Tadalafil was effective and well tolerated in this patient population.

KEY WORDS: penis, penile erection; impotence, drug therapy

Approximately 150 million men worldwide are unable to achieve and maintain an erection adequate for satisfactory sexual performance.[1] Consistent with increasing life expectancies and the age related nature of erectile dysfunction,[2] this population is projected to more than double in the next 25 years.[1] In an epidemiological review focusing on the United States the prevalence of erectile dysfunction has been estimated to be as high as 30 million cases.[3]

The introduction of sildenafil, a phosphodiesterase type 5 inhibitor, transformed the clinical landscape of erectile dysfunction, empowering many men to seek treatment.[4,5] Phosphodiesterase type 5 inhibitors slow metabolism of 3′,5′-cyclic guanosine monophosphate, a second messenger for the smooth muscle relaxing effects of nitric oxide.[6,7] With sexual stimulation, endothelial cells and nonadrenergic, noncholinergic neurons release nitric oxide, which facilitates relaxation of trabecular erectile tissues and dilatation of the helicine artery of the penis through stimulation of cyclic guanosine monophosphate synthesis.[3,8] The resultant increase in flow causes the engorgement of the sinusoidal spaces of the corpora cavernosa with blood. This engorgement causes the tunica albuginea to compress the subtunical venules that drain the corpora and diminish venous outflow from the penis. The penile blood pressure consequently increases, resulting in a physiological erection.[3]

Tadalafil, a potent selective phosphodiesterase type 5 inhibitor, is in development as an oral treatment for erectile dysfunction.[9] We evaluated its efficacy and safety with integrated analyses of findings from 5 randomized, double-blind placebo controlled trials involving men with erectile dysfunction of varying severities and etiologies (table 1).

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Editor's Note: **This article is the first of 5 published in this issue for which category 1 CME credits can be earned. Instructions for obtaining credits are given with the questions on pages 1546 and 1547.**

MATERIALS AND METHODS

Study design. Five randomized, double-blind, placebo controlled, parallel group trials were conducted at 74 centers from April 1999 to April 2001. Following a screening visit

TABLE 1. *Summary of 5 tadalafil studies*

No. Study	No. Centers	Placebo	Tadalafil (mg.)				Totals
			2.5	5	10	20	
1	19	69	—	72	74	—	216
2	18	76	74	79	79	—	308
3	8	66	—	—	65	65	196
4	4	47	—	—	—	93	140
5	25	50	—	—	103	100	253
Totals	74	308	74	151	321	258	1,112

during which a medical history, physical examination and laboratory safety tests including an electrocardiogram were performed, patients who made at least 4 attempts at sexual intercourse during a 4-week treatment-free run-in period were randomly allocated (stratified by baseline severity of erectile function in 1 study) to 12 weeks of treatment with placebo (308) or tadalafil at fixed daily doses of 2.5 mg. (74), 5 mg. (151), 10 mg. (321) or 20 mg. (258). Treatment in 1 study extended to 24 weeks and for the purpose of this analysis data from the 12-week assessment are presented. Patients were instructed to self-administer treatment as needed before sexual intercourse with no restrictions on food or alcohol intake or timing of sexual activity. Patients were seen at 4-week intervals until they completed the study or discontinued early for any reason.

Study population. Men 18 years old or older who had a minimum 3-month history of mild to severe erectile dysfunction of organic, psychogenic or mixed etiology (as determined by the investigator) with a steady female partner were eligible to participate in these studies. Consistent with current United States medical practice, specific diagnostic tests were not required for the clinical diagnosis of erectile dysfunction. We excluded from study patients who failed to achieve erection following radical prostatectomy or pelvic surgery, or had clinically significant penile deformities or penile implants, a recent history of stroke or spinal cord trauma, cardiovascular diseases (for example unstable angina, recent myocardial infarction, recent myocardial revascularization, poorly controlled blood pressure) and/or clinically significant renal or hepatic insufficiency. Men treated with nitrates, antiandrogens or cancer chemotherapy also were excluded from study.

Measures. The effects of tadalafil on erectile function were evaluated using the International Index of Erectile Function (IIEF),[10] Sexual Encounter Profile (SEP) and Global Assessment Question (GAQ). The IIEF is a self-administered questionnaire that assesses 5 domains of male sexual function, including erectile function, orgasmic function, sexual desire, intercourse satisfaction and overall satisfaction. Each of these domains consists of patient ratings of sexual function on 5 to 6-point Likert scales in which higher scores signify better sexual function. The IIEF has been translated into more than 10 languages and cross-culturally validated. It was administered at baseline and following treatment. The SEP diary was recorded by patients after each sexual attempt throughout the study. The GAQ ("Has the treatment you have been taking over the past study interval improved your erections? [yes/no]") was assessed at the end of the study or at the discontinuation visit.

The mean change from baseline to end point on the erectile function domain of the IIEF in each treatment group constituted a primary efficacy outcome measure. The erectile function domain consists of 6 questions and possible scores range from 1 to 30. The other 2 co-primary efficacy variables were the mean changes from baseline to end point in proportions of "yes" responses to 2 yes/no questions in the SEP diary: "Were you able to insert your penis into your partner's vagina?" (SEP-Q2) and "Did your erection last long enough for you to have successful intercourse?" (SEP-Q3).

A number of other efficacy outcomes were also evaluated, including the absolute proportion of affirmative responses to the GAQ, mean change from baseline to end point in the IIEF intercourse satisfaction domain, mean change from baseline to end point in the IIEF overall satisfaction domain, the proportion of patients achieving a final IIEF erectile function domain score of at least 26 (normal erectile function according to Cappelleri et al[11]), the absolute proportion of successful intercourse completion among all sexual attempts (SEP-Q3) and the rate of completion of successful intercourse at distinct post-dose intervals (30 minutes or less, greater than 30 minutes, 4 hours, 4 to 12 hours, greater than 12 to 24 hours, greater than 24 to 36 hours).

Blood samples were collected at each visit for laboratory safety evaluations, including serum chemistry and hematology. Urinalysis and electrocardiogram were obtained at screening and at the final visit. Vital signs were assessed at each visit and patients were followed for possible treatment emergency adverse events, which either first appeared or were exacerbated during the study.

Statistical analysis. All analyses were conducted on an intent-to-treat basis. The analysis of efficacy included all patients who had a baseline measurement and at least 1 post-baseline measurement. The analysis of safety included all randomized patients. Since study design and patient population were consistent across all 5 studies, efficacy and safety data from all 5 studies were pooled for all analyses. Each of the 5 studies was adequately powered to demonstrate statistically significant differences between placebo and tadalafil for each efficacy variable.

ANCOVA models were used to evaluate treatment differences for all continuous outcomes. Changes in proportions were treated as continuous outcomes. Models included terms of treatment group, baseline value, study and baseline by treatment group interaction. In any model, if the interaction was not significant (that is if $p \geq 0.10$), then it was removed from the model and the main effects model remained from which the between treatment group p value was obtained. Pairwise comparisons of active doses versus placebo were based on least-squares means adjusted by the method of Bonferroni. Responses to the GAQ and other categorical outcomes were analyzed using a logistic regression model and included covariate terms described previously.

A subgroup analysis was conducted to evaluate the change from baseline to end point in the erectile function domain according to baseline severity category using an aggregated version of the Cappelleri categorization for severe (scores of 1 to 10), moderate (11 to 16) or mild/normal (17 to 30) erectile dysfunction.[11] Additional subgroup analyses were performed for elderly patients, patients with diabetes and patients with hypertension or on antihypertensive medications. Analyses were conducted using the SAS statistical package (SAS Institute, Cary, North Carolina).

RESULTS

Demographic characteristics. Demographic characteristics of the 1,112 patients were well balanced in each treatment group (table 2). Mean patient age was 59 years (range 22 to 82). Most (90%) had erectile dysfunction for more than a year, and the condition was mild in 41%, moderate in 23% and severe in 36%. Of the patients 61% had organic, 31% mixed and 9% psychogenic erectile dysfunction. Hypertension was present in 30% of men and 21% had diabetes. A total of 995 (89%) of patients completed treatment and 20 (less than 2%) discontinued treatment because of protocol violations (or entry criteria not met).

Efficacy. Tadalafil therapy, particularly at doses of 5 to 20 mg., significantly improved erectile function as assessed by all 3 co-primary and other efficacy outcome variables (table 3). On all efficacy outcomes there was greater numeric improvement with increasing doses of tadalafil. The mean IIEF

TABLE 2. *Demographic and baseline characteristics of men with erectile dysfunction*

	Placebo		Tadalafil (mg.) 2.5		5		10		20		Totals	
No. pts.	308		74		151		321		258		1,112	
Mean pt. age (range)	59 (22–81)		60 (36–79)		59 (26–82)		58 (26–81)		59 (31–80)		59 (22–82)	
No. age greater than 65 (%)	84	(27)	22	(30)	42	(28)	96	(30)	84	(33)	328	(30)
No. duration of erectile dysfunction greater than 12 mo. (%)	276	(90)	67	(91)	137	(91)	280	(87)	239	(93)	999	(90)
No. erectile dysfunction etiology (%):												
Organic	185	(60)	50	(68)	87	(58)	215	(67)	136	(53)	673	(61)
Psychogenic	29	(9)	6	(8)	15	(10)	20	(6)	27	(11)	97	(9)
Mixed	94	(31)	18	(24)	49	(33)	86	(27)	95	(37)	342	(31)
No. IIEF erectile function severity (%):												
Mild (17–30)*	118	(39)	27	(37)	47	(31)	129	(40)	135	(52)	456	(41)
Moderate (11–16)	74	(24)	16	(22)	33	(22)	84	(26)	51	(20)	258	(23)
Severe (1–10)	114	(37)	31	(42)	71	(47)	107	(33)	72	(28)	395	(36)
No. medical history (%):												
Hypertension	93	(30)	23	(31)	51	(34)	90	(28)	72	(28)	329	(30)
Coronary artery disease	24	(8)	10	(14)	10	(7)	18	(6)	24	(9)	86	(8)
Diabetes mellitus	70	(23)	18	(24)	31	(21)	69	(22)	47	(18)	235	(21)
Depression	15	(5)	3	(4)	8	(5)	15	(5)	16	(6)	57	(5)

The cause of erectile dysfunction was determined by the investigators based on patient history, physical examination findings and any previous diagnostic testing.

* Patients were included based on a history of erectile dysfunction, and subsequent assessment of erectile function by the IIEF at baseline revealed that a small proportion of study participants (5%) had an erectile function domain score 26 or greater.

TABLE 3. *Summary of major efficacy variables at end point*

Efficacy Variables	Placebo		Tadalafil (mg.) 2.5		5		10		20		Overall p Value
	End Point	Change	End Point	Change	End Point	Change	End Point	Change	End Point	Change	
Primary											
Mean IIEF erectile function domain	15.1	0.6	16.6	3.2*	17.7	4.6†	21.1	6.5†	23.9	7.9†	<0.001
Mean % of success SEP diary:											
Q2 (achieving erections)	48%	2%	56%	15%†	57%	16%†	73%	24%†	80%	27%†	<0.001
Q3 (maintaining erections)	31%	6%	37%	20%*	40%	22%†	58%	34%†	70%	39%†	<0.001
Secondary											
% GAQ[1] (improved erection)‡	35%	—	42%*	—	50%†	—	67%†	—	81%†	—	<0.001
Mean IIEF:											
Intercourse satisfaction domain	7.4	0.8	7.8	1.6	8.5	1.6†	9.3	2.6†	10.5	3.4†	<0.001
Overall satisfaction domain	5.2	0.5	5.8	0.8	6.1	1.3†	6.7	1.8†	7.4	2.4†	<0.001

* Pairwise comparisons between placebo and treatment $p < 0.05$.
† Pairwise comparison between placebo and treatment $p < 0.001$.
‡ GAQ results for 4, 12-week studies (placebo 261, 2.5 mg. 74, 5 mg. 151, 10 mg. 321, 20 mg. 165).

erectile function domain score increased marginally from baseline to end point on placebo (0.6) compared with changes of 3.2 ($p < 0.05$ versus placebo), 4.6 ($p < 0.001$), 6.5 ($p < 0.001$) and 7.9 ($p < 0.001$) in the tadalafil 2.5, 5, 10 and 20 mg. treatment groups, respectively. Mean changes from baseline to end point in proportions of sexual attempts marked by successful penetration (SEP-Q2) and intercourse completion (SEP-Q3) were significantly increased in each tadalafil treatment group compared with placebo (table 3).

On treatment the absolute proportion of successfully completed sexual attempts, a secondary efficacy outcome, was 75% in men receiving 20 mg. tadalafil compared with 32% on placebo (fig. 1). With regard to other secondary efficacy outcome measures, 81% of men who received 20 mg. tadalafil

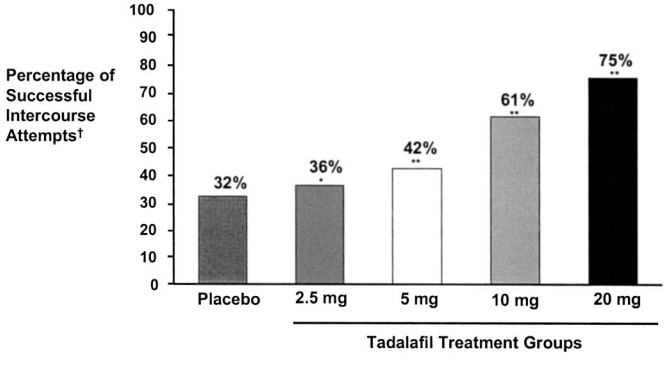

FIG. 1. Effects of tadalafil on successful intercourse attempts (SEP-Q3).

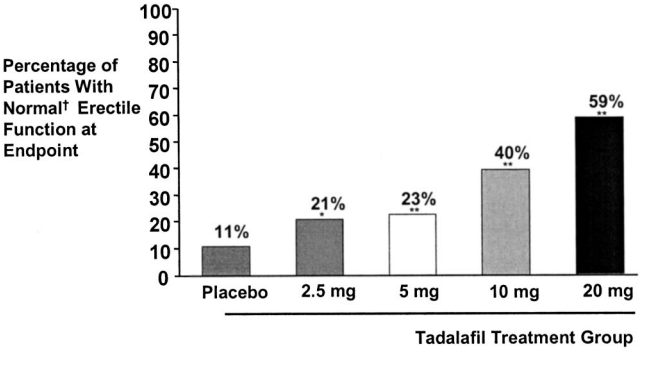

FIG. 2. Percentage of patients with normal erectile function at end point (IIEF).

reported improved erections at end point (GAQ) compared with 35% in placebo controls ($p < 0.001$). Doses of at least 5 mg. tadalafil also significantly improved sexual satisfaction (versus placebo) as assessed by increases from baseline to end point in the intercourse satisfaction and overall satisfaction domains of the IIEF (table 3). Of patients who received 20 mg. tadalafil 59% achieved normal erectile function according to IIEF scores (erectile function domain 26 or greater) at end point compared with 11% of controls ($p < 0.001$) (fig. 2). When the SEP-Q3 was analyzed for selected intervals, a total of 73% to 80% of intercourse attempts between 30 minutes and 36 hours post-dose resulted in successful completion in the 20 mg. tadalafil group (fig. 3).

The baseline severity of erectile dysfunction was a significant factor in all studies, and more severely affected patients tended to experience greater improvement in erectile function. However, within each baseline severity category at least 5 mg. tadalafil significantly augmented mean IIEF erectile function domain scores compared with placebo, and responses to 20 mg. tadalafil were consistently higher than responses to 10 mg. (fig. 4).

Additional analyses demonstrated that the efficacy of tadalafil was similar for patients older than 65 and their younger counterparts. Tadalafil therapy also showed significantly beneficial effects in men with or without baseline diabetes. Compared with control subjects, men with diabetes and erectile dysfunction who received 5 to 20 mg. tadalafil experienced significant improvements from baseline in the IIEF erectile function domain, proportions of successfully completed intercourse attempts (SEP-Q3) and GAQ, with up to 76% of patients reporting improved erections.

Safety results. All doses of tadalafil were well tolerated over the dose range. The most frequently reported treatment emergency adverse events were headache and dyspepsia, followed by back pain, nasal congestion, myalgia and flushing (table 4). These events were mostly mild or moderate and decreased in frequency with continued treatment in most patients. The rate of discontinuation due to adverse events in the tadalafil group was 2.1% compared to 1.3% in controls. Subgroup analyses revealed no differences between the incidences of adverse events in tadalafil treated men 65 years old or older compared with younger men, or between men with or without diabetes mellitus or hypertension, irrespective of concomitant antihypertensive therapy. Tadalafil exerted no clinically significant effects on vision. One tadalafil treated patient (0.1%) reported an episode of abnormal color vision. There were no clinically relevant differences in the incidence of abnormal laboratory changes or electrocardiogram changes between patients treated with placebo or tadalafil.

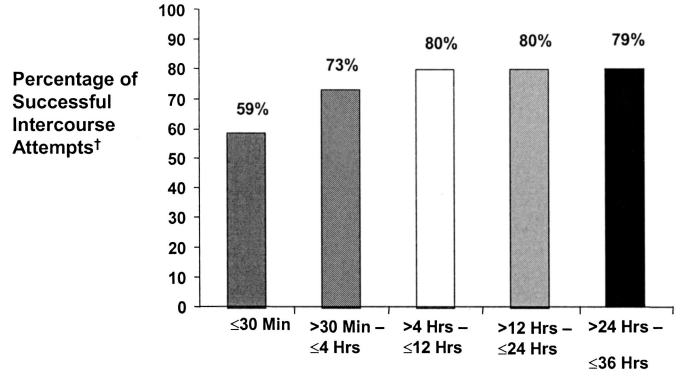

FIG. 3. Effects of tadalafil on successful intercourse completion (SEP-Q3) with time after dosing.

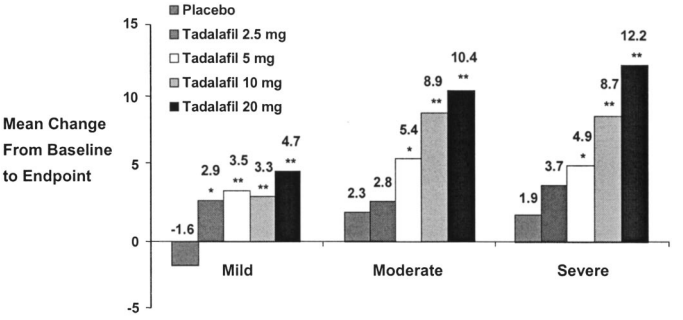

FIG. 4. Changes from baseline in IIEF erectile function domain scores at end point by baseline severity.

DISCUSSION

Treatment with tadalafil, particularly at doses of 10 and 20 mg., significantly improved erectile function in a broad spectrum of patients with erectile dysfunction. The study population in these integrated analyses was similar to that in the Massachusetts Male Aging Study[2] with respect to many demographic variables, including age and the presence of concomitant disease. Mean age of the study population was 59 years, and approximately 30%, 21% and 8% of men had hypertension, diabetes or coronary artery disease, respectively. A history of depression was reported in 5% of men evaluated in these analyses.

Tadalafil provided robust, statistically significant effects across all co-primary efficacy variables. Efficacy increased numerically with increasing dose. Men randomized to 20 mg. tadalafil experienced an increase of 7.9 units in the IIEF erectile function domain, which translated to an increase in the mean score to 23.9 at end point. Mean changes from baseline in proportions of affirmative responses to SEP-Q2 and SEP-Q3 were significantly more marked in the tadalafil groups than controls. In addition, 75% of all intercourse attempts were successfully completed with 20 mg. tadalafil (SEP-Q3).

The efficacy of tadalafil was demonstrated across a broad range of outcomes. At study end point 81% of patients taking 20 mg. tadalafil reported improved erections by a positive response to the GAQ. Analysis of change in the IIEF erectile function domain showed that 59% of these men achieved normal scores at end point ($p < 0.001$ versus placebo). Tadalafil therapy (5 mg. or greater) significantly enhanced the intercourse satisfaction and overall satisfaction domains. These findings are consistent with prior sildenafil trial data[4] and the mechanism of action for phosphodiesterase type 5 inhibitors.

The efficacy of tadalafil was evident without regard to erectile dysfunction etiology or patient age. For instance, among men with diabetes (5 to 20 mg.) tadalafil significantly restored erectile function (versus placebo) as assessed by the IIEF domain, SEP-Q3 and GAQ. These findings were also consistent with a separate randomized, double-blind, placebo controlled study involving 216 men with erectile dysfunction and type 1 or 2 diabetes, which demonstrated that tadalafil significantly improved the erectile function domain of the IIEF from baseline to end point, as well as penetration (SEP-Q2) and successful intercourse completion (SEP-Q3) rates.[12]

Tadalafil, which has a mean terminal half-life of 17.5 hours, exhibited a broad window of therapeutic responsiveness. At a dose of 20 mg. tadalafil enabled 73% to 80% of sexual intercourse attempts to be completed successfully (with appropriate sexual stimulation) between 30 minutes and 36 hours after dosing. These findings were consistent

TABLE 4. *Summary of most commonly reported adverse events and discontinuations from treatment*

Safety Variable	Placebo	All Tadalafil	Tadalafil (mg.)			
			2.5	5	10	20
No. pts.	308	804	74	151	321	258
No. overall safety (%):						
Subjects with greater than 1 treatment emergency adverse events	159 (52)	479 (60)	38 (51)	68 (45)	185 (58)	188 (73)
Discontinuations from adverse events	4 (1.3)	17 (2.1)	3 (4.1)	1 (0.7)	5 (1.6)	8 (3.1)
No. most common treatment emergency adverse events (%):						
Headache	19 (6)	114 (14)	5 (7)	17 (11)	37 (12)	55 (21)
Dyspepsia	7 (2)	81 (10)	1 (1)	7 (5)	28 (9)	45 (17)
Back pain	15 (5)	50 (6)	3 (4)	5 (3)	20 (6)	22 (9)
Rhinitis (nasal congestion)	12 (4)	40 (5)	4 (5)	6 (4)	18 (6)	12 (5)
Myalgia	6 (2)	38 (5)	2 (3)	2 (1)	16 (5)	18 (7)
Vasodilatation (flushing)	6 (2)	30 (4)	1 (1)	4 (3)	11 (3)	14 (5)

with separate placebo controlled clinical trials demonstrating that tadalafil confers significant effects (versus placebo) from 16 minutes to 36 hours after dosing.[13] Tadalafil was administered without restrictions of alcohol and food intake. Along with the period of responsiveness, this lack of restriction of dosing with either alcohol or food will allow for greater convenience and is consistent with certain patient lifestyle needs.[14] Of importance, the therapeutic effects of tadalafil increased as a direct function of baseline erectile dysfunction severity. Therapy with tadalafil was well tolerated, with a low rate of discontinuation due to adverse events (2.1% versus 1.3% of placebo treated patients). The most common untoward effects (for example, headache, dyspepsia) were mostly mild or moderate and transient. There were no significant laboratory abnormalities or electrocardiogram changes.

CONCLUSIONS

Tadalafil therapy, taken as needed before sexual activity and without restrictions on food or alcohol intake, significantly improved erectile function. It allowed a substantial proportion of patients to achieve a normal IIEF erectile function domain score, exhibited a broad window of therapeutic responsiveness and was well tolerated in a representative population of patients with broad-spectrum erectile dysfunction.

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