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Vardenafil for Treatment of Men With Erectile Dysfunction: Efficacy and Safety in a Randomized, Double-Blind, Placebo-Controlled Trial

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Erectile dysfunction (ED) has been reported to affect as many as 20 to 30 million men in the United States and 152 million men worldwide (NIH Consensus Conference, 1993; Feldman et al, 1994; Ayta et al, 1999). The risk for ED increases progressively with advancing age (Feldman et al, 1994). The causes of ED are divided into 3 broad categories: psychogenic, organic, and mixed (Lue, 2000). Although psychogenic factors are involved alone or in combination with organic causes in a substantial number of ED cases (Araujo et al, 1998; Rosen, 2001), organic factors are thought to be involved in the vast majority of ED cases (Levine, 2000). Organic ED results from neurologic, hormonal, or vascular pathologies and may often have drug-related causes (Lue, 2000). ED is commonly associated with a number of other conditions frequently occurring in aging men, including prostatic hypertrophy, arterial hypertension, ischemic heart disease, peripheral vascular disease, atherosclerosis, hyperlipidemia, and diabetes mellitus (Chew et al, 2000; Goldstein, 2000; Lue, 2000).

Local treatments for ED, including vacuum constriction devices, penile self-injection therapy, transurethral alprostadil, and penile prostheses (Derouet and Zehl, 1993; Padma-Nathan et al, 1997; Purvis et al, 1999; Lue, 2000; Montague and Angermeier, 2000), can restore erectile function (EF), but no single therapy is satisfactory for every patient (Meinhardt et al, 1999; Lue, 2000). These treatment options may often limit patient satisfaction because of their invasiveness, unappealing technique, or side effects (Burnett, 1998). Oral treatments used with variable success by men with ED in various countries have included sildenafil, apomorphine, phentolamine, trazodone, and yohimbine.

Orally administered phosphodiesterase 5 (PDE5) inhibitors have become the first-line treatment option for ED. Vardenafil is a potent, highly selective PDE5 inhibitor that shows promise in the oral pharmacotherapy of ED. Vardenafil is rapidly absorbed with a t_{max} as early as 0.7 hour (median, 1 hour) and a $t_{½}$ of approximately 4 hours (Klotz et al, 2001). In a phase 2 study involving 601 men with ED, vardenafil significantly improved erections vs placebo ($P < .001$) (Porst et al, 2001), with the percentage of successful intercourse attempts ranging from 71% to 75%. Among patients taking the 20-mg dose of vardenafil, 80% experienced improved erections. Vardenafil was effective in men with ED of all etiologies and severities and was well tolerated and effective in men who were also taking antihypertensive medications (Porst and Schmidt, 2001). In recently completed phase 3 studies, vardenafil significantly improved EF in men with type 1 or 2 diabetes mellitus (Goldstein et al, 2001), as well as in men with a history of radical prostatectomy (Brock et al, 2002), both of which are challenging to treat populations.

This pivotal study conducted in the United States and Canada was undertaken to determine the efficacy and safety of vardenafil in a broad population of men with ED of various etiologies and severity.

Study Design

This study was conducted in 54 study centers in the United States and Canada. This phase 3, multicenter, randomized, double-blind, placebo-controlled, 4-arm, parallel-group, fixed-dose comparison of vardenafil 5, 10, and 20

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mg vs placebo consisted of 3 phases: 1) a 4-week baseline period in which no treatment or device for ED was allowed; 2) randomization (by random code generation at Bayer Corporation) to 26 weeks of treatment with vardenafil or placebo; and 3) a 1-week follow-up for continued monitoring of adverse events. The study was conducted with Institutional Review Board/Independent Ethics Committee approval and with signed, written, informed consent from all patients.

Inclusion Criteria

Eligible patients were men 18 years of age or older experiencing ED, which was defined as the inability to achieve or maintain a penile erection sufficient for satisfactory sexual intercourse, for more than 6 months in duration. To be enrolled in the treatment phase of the study, patients were required to have experienced a 50% or greater failure rate in maintaining an erection sufficient to complete intercourse on at least 4 separate attempts over the 4-week treatment-free baseline period.

Exclusion Criteria

Conditions that precluded study entry included anatomic abnormalities of the penis that could impair EF, hypoactive sexual desire, a history of radical prostatectomy, ED after spinal cord injury, retinitis pigmentosa, unstable angina pectoris, uncontrolled atrial tachyarrhythmia, or, within the previous 6 months, any myocardial infarction, stroke, electrocardiographic ischemia, or life-threatening arrhythmia. Patients were excluded if they had symptomatic postural hypotension within 6 months prior to screening, resting hypotension (systolic blood pressure [SBP] $<$90 mm Hg), hypertension (resting SBP $>$170 mm Hg or diastolic blood pressure [DBP] $>$110 mm Hg), a history of hepatitis B surface antigen or hepatitis C, severe chronic liver disease or abnormalities, chronic hematologic disease, bleeding disorder, poorly controlled diabetes mellitus (hemoglobin A1c $>$12%), inadequately treated hyperthyroidism or hypothyroidism, or a history of peptic ulcer disease within 1 year of screening. Also excluded were patients with a history of malignancy within the previous 5 years, low serum testosterone levels (defined as the lower limit of normal, according to the range of laboratories that participated in the study, which was at least 10 nmol/L), serum creatinine values $>$2.5 mg/dL, any investigational drug usage within 30 days of screening, and sildenafil or other therapy for ED within 7 days of screening. Previous sildenafil treatment was allowed if patients reported improvements in EF while on sildenafil. Nitrate medication was strictly contraindicated. Antiandrogens, anticoagulants, androgens, and trazodone hydrochloride were not allowed.

Treatment

Patients were instructed to take study medication approximately 1 hour before intended sexual intercourse and were given no special instruction in regard to food or alcohol use. Not more than a single dose of the study drug was permitted per calendar day. Medication use was monitored from the patients' medication/outcome diaries and pill counts performed by study personnel during assessment visits.

Efficacy Variables

The intent-to-treat (ITT) population consisted of all patients who had received at least 1 dose of study medication and who had received at least 1 efficacy assessment. The primary efficacy measures were EF domain score (questions 1–5 and 15) of the International Index of Erectile Function (IIEF) questionnaire after 12 weeks of treatment and patients' responses to 2 diary questions (''Were you able to insert your penis into your partner's vagina?'' and ''Did your erection last long enough for you to have successful intercourse?''). The mean success rate for each patient was calculated from the start of the study drug to week 12, the a priori primary endpoint. In addition, as secondary endpoints, these variables were determined at weeks 4, 8, 18, and 26. The additional secondary efficacy measure reported here was the response by patients completing weeks 12 and 26 of treatment to the following Global Assessment Question (GAQ): (''Has the treatment you have taken over the past 4 weeks improved your erections?'').

Safety

All patients who had received at least 1 dose of study medication and had postbaseline safety data were evaluated for adverse events. For each adverse event, the investigator assessed its seriousness, intensity (mild, moderate, or severe), and relationship to study medication (none, unlikely, possible, probable, or indeterminate). A full physical examination was performed at screening, and abbreviated examinations (including a 12-lead electrocardiogram) were performed at weeks 12 and 26 following commencement of therapy. Routine laboratory tests and vital sign determinations were performed at screening, at baseline, and during treatment (weeks 4, 12, 18, and 26 or at premature discontinuation). On certain office visits, patients were asked to take vardenafil prior to being seen in the office in order to take measurements within an optimal window of drug activity defined as 11 minutes to 5 hours after oral ingestion.

Statistical Methods: Efficacy Analysis

The primary IIEF efficacy variables were tabulated, followed by analysis of covariance testing with baseline values as a covariate and terms for center and treatment. The interactions between treatment and center by treatment were determined to be insignificant. Testing of hypotheses included comparisons of each vardenafil dosage group vs placebo; therefore, a Bonferroni adjustment was used, with statistical significance being considered a *P* value

less than .0167. Least-squares mean EF domain scores were assessed as last observation carried forward (LOCF) to account for patient dropouts. The mean value for each treatment group was calculated from each individual's success rate for each diary question. Responses to the GAQ were analyzed using logistic regression. Retrospective analysis was also performed to determine the percentage of patients reaching EF domain scores consistent with normal EF (≥26), stratified by treatment group and baseline EF score (Cappelleri et al, 1999). Statistical significance was defined as *P* less than or equal to .05 for all secondary efficacy variables.

The number of patients evaluated in this study was based on all 3 primary efficacy variables. Sample size calculations assumed a standard deviation of 10.3 for EF domain scores and 35% for the diary questions. Treatment differences considered to be clinically significant were 5 points for the EF domain score and 18% for the diary questions. With approximately 143 valid patients per group, this study had the power of approximately 95% for the EF domain score and the power of approximately 97.5% for the diary questions. This yielded a lower bound to the power of the study of 90%. Allowance of a 10% dropout rate in the first month required 159 randomized patients for the efficacy analysis. However, to obtain 6-month safety data on 150 patients at the highest dose, the number of patients randomized was increased to 200 patients per group (assuming an overall 25% dropout rate).

Statistical Methods: Safety Analysis

Rates of discontinuations, adverse events, and laboratory and electrocardiographic abnormalities, as well as measurements and changes from baseline in blood pressure and heart rate, were recorded.

Patient Population and Demographics

This study was conducted from March 29, 2000 (first patient, first visit), to March 2, 2001 (last patient, last visit). Eight hundred five men at 54 study centers completed baseline evaluations and were randomized to treatment with either placebo (n = 197) or vardenafil 5 mg (n = 205), 10 mg (n = 206), or 20 mg (n = 197). Over the course of 26 weeks of therapy, 37% of all patients (297 of 805) discontinued (Figure 1). Of patients randomized to placebo, 54% discontinued, most commonly because of insufficient therapeutic effect (20%). Of patients randomized to vardenafil, 31% discontinued, with the most common cause being insufficient therapeutic effect (13%) in the 5-mg group, lost to follow-up (10%) in the 10-mg group, and adverse events (8%) in the 20-mg group. Seven hundred sixty-two men were valid for safety, and 749 men were valid for the ITT analysis.

At baseline, there were no clinically meaningful differences between treatment groups with respect to any demographic or clinical variables (Table 1). Overall, patients were diagnosed with ED a mean of 3.6 years prior to screening and experienced symptoms of ED an average of 2.3 years before the clinical diagnosis was made (time of first noticed ED minus time since ED first diagnosed). Sildenafil had been used previously by 71% (544 of 762), all of whom experienced improved erections during this treatment. Only 15 of 506 screening failures were due to failure to respond to sildenafil. Prior use of other medications for ED or devices for erectile enhancement was infrequent. The treatment groups were well balanced in terms of medical history (Table 1). Findings at screening with overall rates greater than 10% were hypertension (37%), pure hypercholesterolemia (24%), prostatic hyperplasia (20%), type 2 diabetes (18%), esophageal reflux (12%), and allergy (12%).

Efficacy: EF Domain, Penetration Success, and Intercourse Completion

At baseline, the mean EF domain score ranged between 13 and 14 and was consistent with moderate ED. At baseline, less than 10% of patients had mild ED, while the proportion of patients with severe ED ranged between 30% and 45% of the population in each treatment arm (Table 1).

The primary efficacy measures, the EF domain and mean success rates of penetration and maintained erections to completion of intercourse after 12 weeks of treatment, indicated significant superiority of all vardenafil doses over placebo ($P < .0001$) (Figures 2 and 3). For those receiving vardenafil 20 mg, the mean EF domain score increased from 12.8 at baseline to 21.4 at week 12, the mean successful penetration rate increased from 40.9% at baseline to 80.5% at week 12, and the mean ability to maintain an erection for successful intercourse increased from 14.7% at baseline to 64.5% at week 12. Similar results were obtained for comparisons of EF domain items and diary responses at other postbaseline assessments. All groups showed continued improvements vs baseline throughout the 26-week treatment period, and differences between scores for placebo-treated patients and those randomized to vardenafil remained significant at 26 weeks ($P \leq .001$).

Improvements in primary efficacy scores were dose related. Notably, at week 12 following randomization, improvements in EF domain scores were significantly higher for the 10- and 20-mg vardenafil dosing groups than for the 5-mg group ($P < .01$ and $P < .001$, respectively). The superior efficacy of vardenafil 10 and 20 mg over the 5-mg dose was maintained at week 26 ($P < .0001$).

Efficacy: Return to Normal EF

The ability of vardenafil to bring patients with ED to normal function (EF domain score ≥26) was apparent irrespective of baseline severity (Figure 4). For patients having mild ED (EF domain scores of 22–25), between 79% and 89% of those receiving vardenafil 20 and 10 mg, respectively, returned to normal function. Importantly,

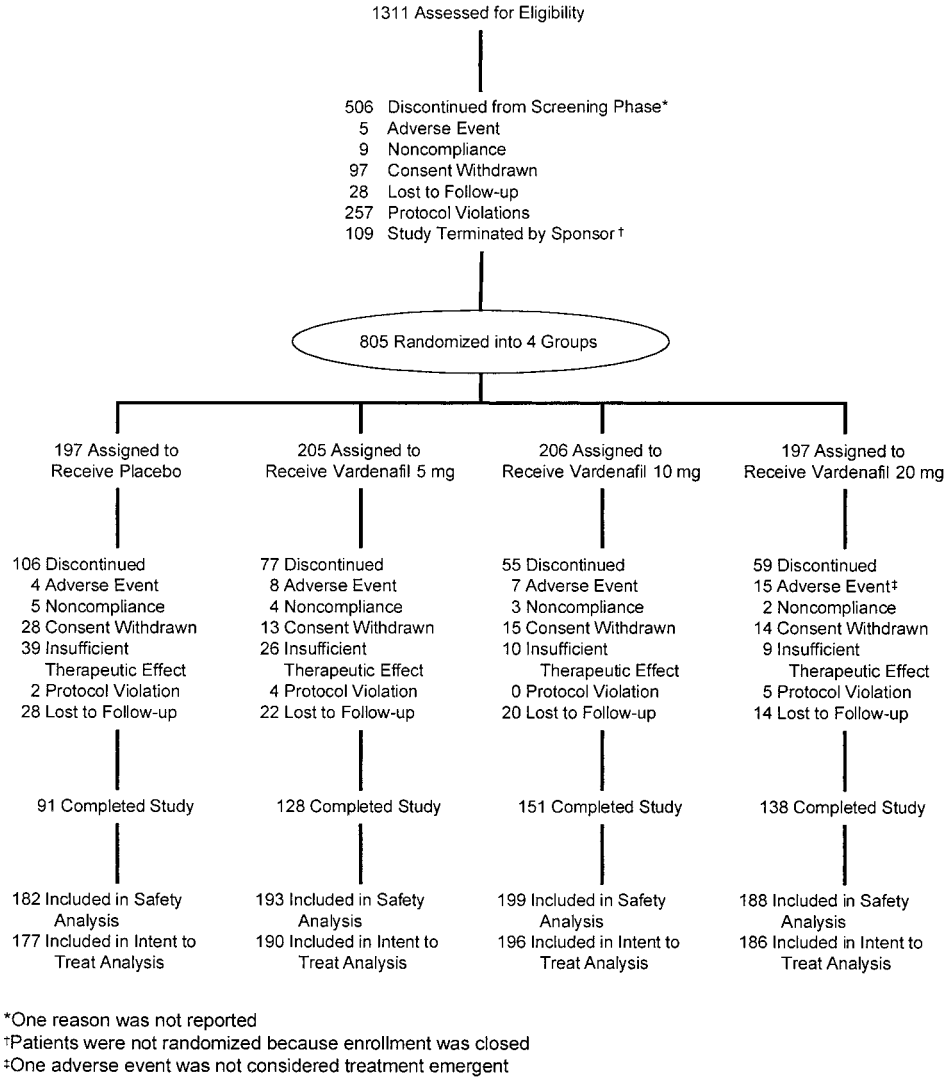


Figure 1. Progress of patients and distribution of randomized patients.

39% of patients with severe ED (EF domain scores ≤10) achieved normal EF after receiving 20 mg vardenafil compared to only 4% on placebo.

Efficacy: GAQ

The proportion of responders, defined as those in the ITT population who affirmatively answered the GAQ, was significantly higher for all groups of patients treated with vardenafil than for those treated with placebo ($P < .0001$) (Figure 5). For this variable, there was also a dose-related difference in response between 5, 10, and 20 mg. At 12 weeks, 64.5% of those receiving vardenafil 5 mg, 72.9% of those receiving vardenafil 10 mg, and 80.9% of those receiving vardenafil 20 mg described a positive response to the GAQ vs 38.6% of those receiving placebo ($P \leq .0001$). Corresponding results for those who completed 26 weeks of therapy were 64.9% for those who received 5 mg vardenafil, 79.8% for those who received 10 mg vardenafil, and 85.2% for those who received 20 mg vardenafil compared with 27.6% of men who received placebo (Figure 5).

Safety

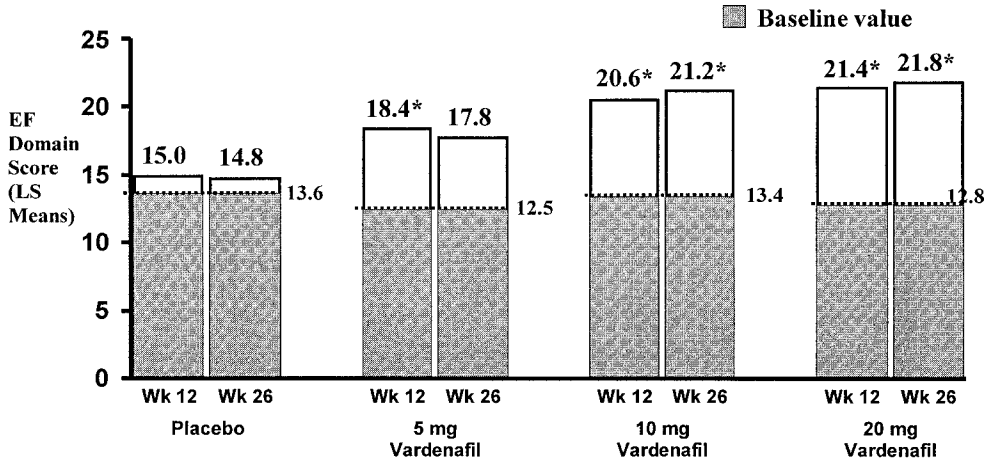
In general, treatment with vardenafil was well tolerated. Most of the treatment-emergent adverse events (TEAEs), regardless of cause, were mild or moderate in intensity. The incidence of TEAEs considered possibly or probably related to study treatment increased with the vardenafil dosage with 7%, 19%, 33%, and 42% for patients treated with placebo or vardenafil 5, 10, or 20 mg, respectively. The most commonly reported TEAEs included headache, rhinitis, cutaneous flushing, and dyspepsia and are shown in Table 2. No type of visual change occurred in more than 2% of patients, with no blue color vision reported.

The incidence of serious TEAEs was nearly constant across all groups: 5%, 5%, 3%, and 4% of patients treated

Table 1. *Demographic and erectile dysfunction (ED) characteristics of patients (safety population)**

		Vardenafil		
	Placebo (n = 182)	5 mg (n = 193)	10 mg (n = 199)	20 mg (n = 188)
Age at enrollment, mean y	57	57	57	58
Race, % Caucasian	77	77	80	82
Time since first noticed ED, mean y	5.1	5.9	6.0	6.6
Time since ED first diagnosed, mean y	2.9	3.6	3.6	4.2
BMI, mean kg/m2	28.8	29.4	28.4	28.7
% Married	80	74	76	77
Severity, IIEF EF score, n (%)†				
Severe (≤10)	53 (30)	86 (45)	71 (36)	78 (42)
Moderate (11–16)	65 (37)	41 (22)	61 (31)	52 (28)
Mild–Moderate (17–21)	44 (25)	50 (26)	51 (26)	39 (21)
Mild (22–25)	15 (8)	11 (6)	9 (5)	14 (7)
Normal (≥26)	0 (0)	2 (1)	4 (2)	3 (2)
Etiology, n (%)				
Organic	98 (54)	117 (61)	118 (59)	112 (60)
Psychogenic	17 (9)	13 (7)	14 (7)	14 (7)
Mixed	67 (37)	63 (33)	67 (34)	62 (33)
Prior sildenafil use, n (%)	124 (68)	149 (77)	147 (74)	124 (66)
Current alcohol consumption, % yes	72	69	75	66
Smoking history, % nonsmoker	38	40	39	45
Medical history, n (%)				
Hypertension	58 (32)	74 (38)	75 (38)	73 (39)
Prostatic hyperplasia	30 (16)	33 (17)	43 (22)	44 (23)
Diabetes type 2	35 (19)	31 (16)	35 (18)	37 (20)
Depression	12 (7)	12 (6)	13 (7)	9 (5)
Prior MI	9 (5)	5 (3)	4 (2)	9 (5)
Hyperlipidemia	7 (4)	12 (6)	14 (7)	14 (7)
Obesity	5 (3)	5 (3)	7 (4)	4 (2)

* BMI indicates body mass index; ED, erectile dysfunction; EF, erectile function domain; IIEF, International Index of Erectile Function; and MI, myocardial infarction.
† Intent-to-treat (ITT) population.



IIEF = International Index of Erectile Function; EF = erectile funct ion;
ITT = intent-to-treat; LOCF = last observation carried forward;
LS = least square; *$P<0.0001$, †$P<0.001$ versus placebo

Figure 2. Efficacy of vardenafil: erectile function (EF) domain scores at baseline and at 12 and 26 weeks of treatment (intent-to-treat [ITT] population, last observation carried forward [LOCF] analysis).

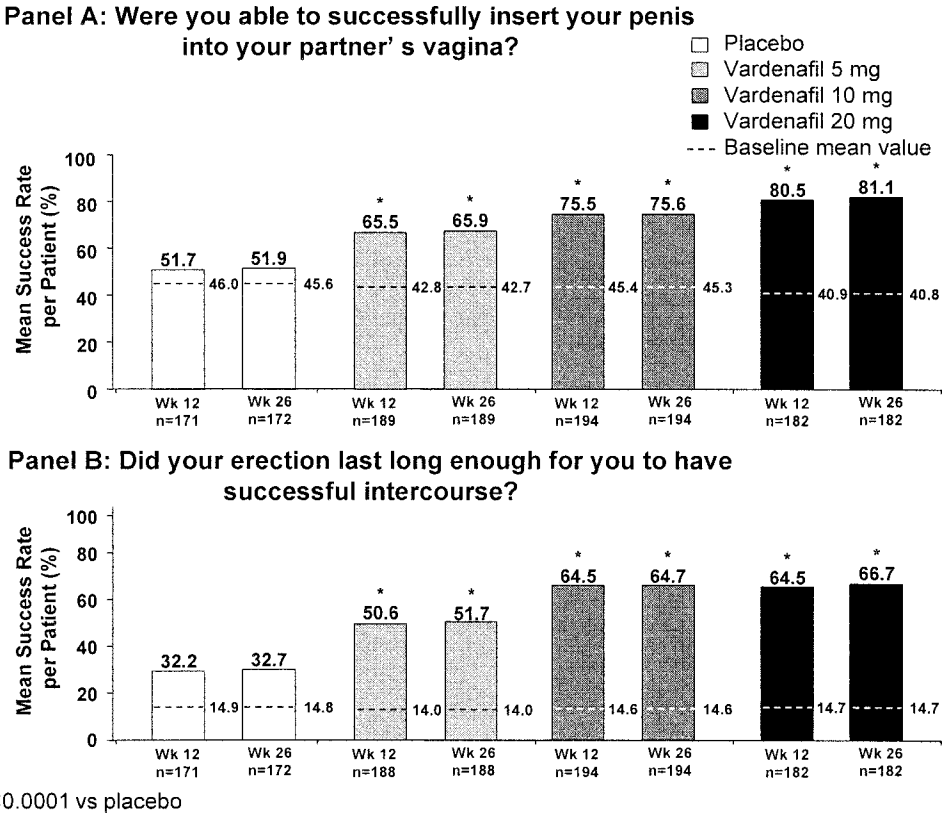
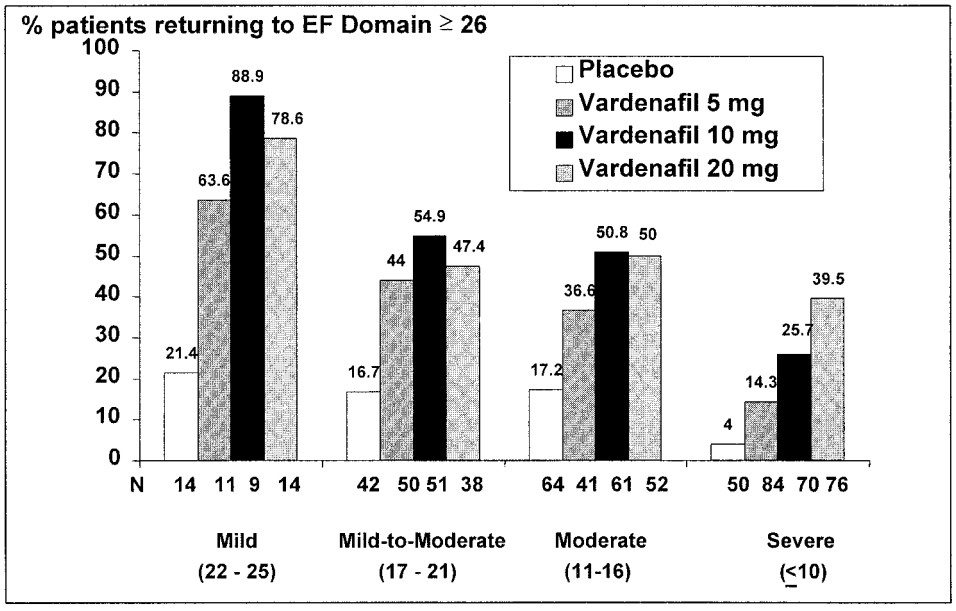
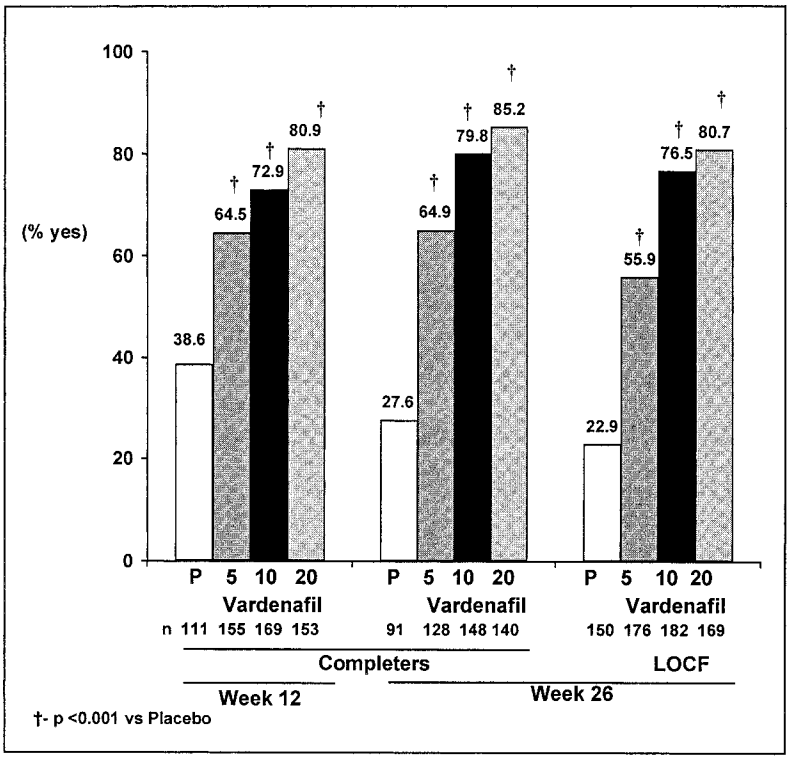


Figure 3. Mean success rates per patient describing ability to penetrate partner **(A)** and maintain erections sufficiently to have successful intercourse **(B)**.



IIEF = International Index of Erectile Function; EF = erectile function;
ITT = intent-to-treat; LOCF = last observation carried forward;

Figure 4. Percentage of patients returning to normal erectile function (EF) (EF domain scores ≥26), stratified by baseline erectile dysfunction (ED) severity (intent-to-treat [ITT] population, last observation carried forward [LOCF]).



ITT = intent-to-treat; LOCF = last observation carried forward;

Figure 5. Percentage of patients responding ''yes'' to the general assessment question ''Did your treatment improve your erections over the past 4 weeks?'' (intent-to-treat [ITT] population). Estimated value from logistic regression analysis.

with placebo or vardenafil 5, 10, or 20 mg, respectively. One myocardial infarction was reported, which occurred in a patient receiving placebo; no deaths were reported in this study. Discontinuations due to adverse events were infrequent and not obviously related to vardenafil dose (Figure 1). Very few single adverse events led to discontinuations of study medication in more than 1 patient per group (headache [2 patients receiving vardenafil 5 or 20 mg], abnormal liver function tests [3 patients receiving vardenafil 10 mg], nausea [2 patients receiving vardenafil 20 mg], hypesthesia [2 patients receiving vardenafil 10 mg], and kidney calculus [2 patients receiving vardenafil 20 mg]).

Table 2. *Incidence of treatment-emergent adverse events during 6 months of study in which incidence is greater than 5% in any treatment group (safety population) and greater than placebo*

	Placebo, n (%) n = 182	Vardenafil, n (%) 5 mg n = 193	10 mg n = 199	20 mg n = 188
Headache	8 (4)	19 (10)	44 (22)	40 (21)
Rhinitis	9 (5)	17 (9)	27 (14)	32 (17)
Cutaneous flushing	0 (0)	9 (5)	20 (10)	24 (13)
Dyspepsia	1 (<1)	2 (1)	8 (4)	12 (6)
Sinusitis	2 (1)	10 (5)	6 (3)	9 (5)
Accidental injury	5 (3)	11 (6)	7 (4)	8 (4)
Flu syndrome	2 (1)	10 (5)	5 (3)	3 (2)

Clinical laboratory evaluations revealed sporadic occurrences of low or high values outside the normal range at some interval during the course of treatment, but no clear dose or group relationship was observed. Analysis of laboratory values, changes from baseline, and time-dependent alterations during the 26-week treatment period indicated no relationship between vardenafil treatment and any laboratory abnormalities.

Analysis of vital signs revealed only minor changes from baseline that were generally similar across treatment groups. Mean changes from baseline in heart rate, measured within 11 minutes and 5 hours after taking the treatment, were minor and appeared unrelated to the dose of vardenafil. Mean blood pressure decreases in patients taking 5, 10, or 20 mg vardenafil were small, ranging from −3.6 to −6.6 mm Hg for supine SBP, from −3.5 to −6.5 mm Hg for standing SBP, from −3.5 to −4.8 mm Hg for supine DBP, and from −2.1 to −4.5 mm Hg for standing DBP. For placebo, changes in baseline were −0.4 mm Hg for supine and standing SBP, −0.7 for supine DBP, and −1.3 for standing DBP.

The percentage of patients with electrocardiographic abnormalities was similar across treatment groups; there was no evidence of an increase in abnormalities from pla-

cebo to vardenafil 20 mg and no clinically notable differences in electrocardiographic parameters between the vardenafil groups and the placebo group. Results obtained within 5 hours of dosing indicated no dose-dependent abnormalities in electrocardiographic parameters. Moreover, at the 26-week visit, changes from baseline in PR, QRS, and QT intervals were similar across all treatment groups.

Comment

The results of this study indicate that vardenafil dosages of 5, 10, and 20 mg were significantly superior to placebo for the treatment of ED, on the basis of the primary study endpoints of the EF domain score of the IIEF and diary-recorded success rates for penetration and maintenance of erection during intercourse. In addition, all vardenafil doses were nearly always significantly superior to placebo on the basis of the secondary study endpoints and the GAQ. For those receiving vardenafil 20 mg, the mean EF domain score increased from 12.8 (moderate, on average) at baseline to 21.4 (mild level of ED, on average) at week 12. Of note, in patients taking 20 mg vardenafil, the per-patient success rate of penetration nearly doubled from 41% at baseline to 80% at week 12, and the ability to maintain an erection for successful intercourse increased fourfold from 15% at baseline to 65% at week 12 (all $P < .0001$ vs placebo). In addition, 81% of those receiving vardenafil 20 mg gave a positive response to the GAQ at week 12 vs 39% of those receiving placebo ($P < .0001$). Efficacy was maintained over the next 14 weeks, resulting in 85% of men using vardenafil 20 mg having reported improved erections at 26 weeks. Importantly, vardenafil 20 mg enabled a considerable percentage of patients to achieve normal EF: 79% of patients with mild ED and up to 39% of patients with severe ED who received vardenafil 20 mg achieved normal EF (based on EF domain scores $\geq$26) (Cappelleri et al, 1999).

The results of the current study extend previous findings for vardenafil. Pharmacokinetic/pharmacodynamic studies demonstrated the rapid absorption of vardenafil and a doubling of the duration of penile rigidity over placebo (Klotz et al, 2001; Stark et al, 2001). In phase 2 studies, vardenafil 5, 10, and 20 mg significantly improved erectile functioning, including vaginal penetration and maintenance of erection, in men with mild to severe ED of all etiologies (Porst et al, 2001). Vardenafil has also been shown to be effective in men with either type 1 or 2 diabetes mellitus (Goldstein et al, 2001).

Vardenafil was well tolerated. The adverse events noted most often with its use—headache, rhinitis, cutaneous flushing, and dyspepsia—were expected based on the pharmacology of PDE5 inhibitors and on clinical trials with other PDE5 inhibitors (Padma-Nathan et al, 2001; Padma-Nathan and Giuliano, 2001). Importantly, only small percentages of patients discontinued during the 6-month study period because of adverse events. These results are consistent with those previously reported for vardenafil (Porst et al, 2001). Nearly all of the adverse events recorded for patients in the trial reported here were mild or moderate in severity and typically resolved with continued use of vardenafil.

Although PDE5 inhibitors have demonstrated good safety and tolerability in a large number of controlled clinical trials, as well as in clinical practice, the vasodilatory effects of these drugs may have safety implications in patients with ED and cardiovascular disease. In this study, changes in vital signs with vardenafil were minor and were generally similar across treatment groups.

There are 2 potential limitations of this study. First, patients with a history of failing sildenafil therapy were specifically excluded from the trial. However, this represented only 15 of 257 men who were specifically excluded by the study investigators prior to randomization. It is therefore unlikely that exclusion of this low percentage of subjects from the study would have significantly affected the overall study findings. The second limitation may be the imbalance between the large number of patients in the placebo group who discontinued because of lack of treatment efficacy and the much smaller number of vardenafil-treated patients who stopped treatment for this reason. This difference could potentially have biased the results to demonstrate a placebo effect in those patients completing the study. However, for the measurement of the EF domain, the LOCF approach to analysis of the data was employed to address this limitation.

In conclusion, in a broad population of men with ED of various etiologies and severity, vardenafil safely and consistently improved all efficacy parameters of EF, improving erections and satisfaction in up to 85% of men treated for 26 weeks and restoring normal EF in up to 89% of men with mild ED and in 39% of men with severe ED.

Acknowledgments

Data Access and Responsibility: All authors of this study have had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis (see accompanying statements).

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References

Araujo AB, Durante R, Feldman HA, Goldstein I, McKinlay JB. The relationship between depressive symptoms and male erectile dysfunction: cross-sectional results from the Massachusetts Male Aging Study. *Psychosom Med.* 1998;60:458–465.

Ayta IA, McKinlay JB, Krane RJ. The likely worldwide increase in erectile dysfunction between 1995 and 2025 and some possible policy consequences. *BJU Int.* 1999;84:50–56.

Brock G, Taylor T, Seger M, for the Vardenafil PROSPECT Group. Efficacy and tolerability of vardenafil in men with erectile dysfunction following radical prostatectomy. *Eur Urol.* 2002;1:152.

Burnett AL. Erectile dysfunction: a practical approach for primary care. *Geriatrics.* 1998;53:34–35, 39–40, 46–48.

Cappelleri JC, Rosen RC, Smith MD, Mishra A, Osterloh IH. Diagnostic evaluation of the erectile function domain of the International Index of Erectile Function. *Urology.* 1999;54:346–351.

Chew KK, Earle CM, Stuckey BG, Jamrozik K, Keogh EJ. Erectile dysfunction in general medicine practice: prevalence and clinical correlates. *Int J Impot Res.* 2000;12:41–45.

Derouet H, Zehl U. Treatment of erectile dysfunction with vacuum pumps. *Urologe A.* 1993;32:312–315.

Feldman HA, Goldstein I, Hatzichristou DG, Krane RJ, McKinlay JB. Impotence and its medical and psychosocial correlates: results of the Massachusetts Male Aging Study. *J Urol.* 1994;151:54–61.

Goldstein I. The mutually reinforcing triad of depressive symptoms, cardiovascular disease, and erectile dysfunction. *Am J Cardiol.* 2000;86: 41F–45F.

Goldstein I, Young JM, Fischer J, et al. Vardenafil, a highly selective PDE5 inhibitor, improves erectile function in patients with diabetes mellitus. *Diabetes.* 2001;50(suppl 2):924.

Klotz T, Sachse R, Heidrich A, et al. Vardenafil increases penile rigidity and tumescence in erectile dysfunction patients: a RigiScan and pharmacokinetic study. *World J Urol.* 2001;19:32–39.

Levine LA. Diagnosis and treatment of erectile dysfunction. *Am J Med.* 2000;109(9 suppl 1):3–12.

Lue TF. Erectile dysfunction. *N Engl J Med.* 2000;342:1802–1813.

Meinhardt W, Kropman RF, Vermeij P. Comparative tolerability and efficacy of treatments for impotence. *Drug Saf.* 1999;20:133–146.

Montague DK, Angermeier KW. Future considerations: advances in the surgical management of erectile dysfunction. *Int J Impot Res.* 2000; 12(suppl 4):S140–S143.

National Institutes of Health (NIH) Consensus Conference. Impotence. NIH Consensus Development Panel on Impotence. *JAMA.* 1993;270: 83–90.

Padma-Nathan H, Giuliano F. Oral drug therapy for erectile dysfunction. *Urol Clin North Am.* 2001;28:321–334.

Padma-Nathan H, Hellstrom WJ, Kaiser FE, et al. Treatment of men with erectile dysfunction with transurethral alprostadil. Medicated Urethral System for Erection (MUSE) Study Group. *N Engl J Med.* 1997;336: 1–7.

Padma-Nathan H, McMurray JG, Pullman WE, et al. On-demand IC351 (Cialis) enhances erectile function in patients with erectile dysfunction. *Int J Impot Res.* 2001;13:2–9.

Porst H, Rosen R, Padma-Nathan H, et al. The efficacy and tolerability of vardenafil, a new selective phosphodiesterase type 5 inhibitor, in patients with erectile dysfunction: the first at-home clinical trial. *Int J Impot Res.* 2001;13:192–199.

Porst H, Schmidt AC, and the Vardenafil Study Group. Vardenafil improved erectile function regardless of age, baseline severity and antihypertensive medication. *Int J Impot Res.* 2001;13(suppl 5):S64.

Purvis K, Egdetveit I, Christiansen E. Intracavernosal therapy for erectile failure—impact of treatment and reasons for drop-out and dissatisfaction. *Int J Impot Res.* 1999;11:287–299.

Rosen RC. Psychogenic erectile dysfunction. Classification and management. *Urol Clin North Am.* 2001;28:269–278.

Stark S, Sachse R, Liedl T, et al. Vardenafil increases penile rigidity and tumescence in men with erectile dysfunction after a single oral dose. *Eur Urol.* 2001;40:181–190.