ORIGINAL CONTRIBUTION

Sildenafil for Treatment of Erectile Dysfunction in Men With Diabetes

A Randomized Controlled Trial

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Context Erectile dysfunction is common in men with diabetes.

Objective To assess the efficacy and safety of oral sildenafil citrate in the treatment of erectile dysfunction in men with diabetes.

Design A multicenter, randomized, double-blind, placebo-controlled, flexible dose-escalation study conducted May through November 1996.

Setting Patients' homes and 19 clinical practice centers in the United States.

Patients A total of 268 men (mean age, 57 years) with erectile dysfunction (mean duration, 5.6 years) and diabetes (mean duration, 12 years).

Interventions Patients were randomized to receive sildenafil (n = 136) or placebo (n = 132) as needed, but not more than once daily, for 12 weeks. Patients took the study drug or placebo 1 hour before anticipated sexual activity. The starting dose of sildenafil citrate was 50 mg, with the option to adjust the dose to 100 mg or 25 mg based on efficacy and tolerability, to be taken as needed.

Main Outcome Measures Self-reported ability to achieve and maintain an erection for sexual intercourse according to the International Index of Erectile Function and adverse events.

Results Two hundred fifty-two patients (94%) completed the study (131/136 in the sildenafil group, 121/132 in the placebo group). By intention-to-treat analysis, at 12 weeks, 74 (56%) of 131 patients in the sildenafil group reported improved erections compared with 13 (10%) of 127 patients in the placebo group ($P<.001$). The proportion of men with at least 1 successful attempt at sexual intercourse was 61% (71/117) for the sildenafil group vs 22% (25/114) for the placebo group ($P<.001$). Adverse events related to treatment were reported for 22 (16%) of 136 patients taking sildenafil and 1 (1%) of 132 patients receiving placebo. The most common adverse events were headache (11% sildenafil, 2% placebo), dyspepsia (9% sildenafil, 0% placebo), and respiratory tract disorder (6% sildenafil, 2% placebo), predominantly sinus congestion or drainage. The incidence of cardiovascular adverse events was comparable for both groups (3% sildenafil, 5% placebo).

Conclusion Oral sildenafil is an effective and well-tolerated treatment for erectile dysfunction in men with diabetes.

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DIABETES MELLITUS AFFECTS AN estimated 15.7 million people in the United States, including 7.5 million men, with type 2, non–insulin-dependent, diabetes accounting for 90% to 95% of the diagnosed cases and type 1, insulin-dependent, diabetes accounting for 5% to 10%.[1] A common complication of diabetes in men is erectile dysfunction (ED), defined by the National Institutes of Health Consensus Panel on Impotence as the persistent inability to attain and maintain an erection sufficient to permit satisfactory sexual activity.[2]

The prevalence of ED of any degree in men aged 40 to 70 years was estimated to be 52% in the Massachusetts Male Aging Study (MMAS), with a prevalence of 25% for moderate ED and 10% for complete ED (ie, no erections).[3] The prevalence of ED is age dependent, with the rate of complete ED increasing from 5% among men aged 40 years to 15% among those aged 70 years.[3]

Erectile dysfunction in men with diabetes is often associated with diabetic neuropathy and peripheral vascular disease.[4,5] It occurs at an earlier age in men with diabetes than in men

See also p 465.

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in the general population,[6,7] and several studies have demonstrated a high prevalence (35% to 75%) of ED with diabetes.[6,8-10] In men with treated diabetes in the MMAS, the age-adjusted prevalence of complete ED (no erections) was 28%, which was approximately 3 times higher than the prevalence of complete ED observed in the entire sample of men (10%).[3]

Penile erection is a hemodynamic event dependent on the relaxation of smooth muscle cells and arteries of the corpus cavernosum.[11] Relaxation of corpus cavernosal smooth muscle is mediated by nitric oxide–induced cyclic 3′, 5′-guanosine monophosphate (cGMP) formation.[12-14] In response to sexual stimuli, nonadrenergic, noncholinergic nerves and endothelial cells of the arterioles in the penis release nitric oxide, which induces smooth muscle relaxation via stimulation of guanylate cyclase and the production of cGMP. Subsequently, cGMP is hydrolyzed by cGMP-specific phosphodiesterase type 5 (PDE5), the predominant PDE isozyme of the corpus cavernosum.[15]

Sildenafil citrate is an orally active and selective inhibitor of PDE5. When sexual stimulation causes local release of nitric oxide, sildenafil enhances the effect of nitric oxide on the corpus cavernosum by increasing the levels of cGMP in this tissue. Sildenafil is rapidly absorbed following oral administration, has an onset of action within 25 to 60 minutes after dosing,[15] and has a plasma half-life of approximately 4 hours.

Sildenafil has been shown to be an effective and well-tolerated treatment in patients with ED of various etiologies.[16] The purpose of the present study was to assess the efficacy and safety of sildenafil in the treatment of ED in men with diabetes. In a pilot study of 21 men with ED and diabetes, treatment with sildenafil improved erectile function, as assessed by penile plethysmography in a clinic setting.[17] This study evaluated sildenafil in a larger population of men with ED and diabetes in a home setting, which reflects the situation encountered in clinical practice.

METHODS

Study Design and Patient Population

The protocol for this multicenter, randomized, double-blind, placebo-controlled, flexible-dose study was approved by the institutional review boards at the 19 clinical practice centers, and all participants provided written informed consent. The study consisted of a 4-week, no-treatment, run-in phase, followed by a 12-week, double-blind treatment period. Sildenafil citrate (Viagra) and placebo of matching appearance were supplied by Pfizer Inc. Patients were instructed to take a single dose of study medication as needed, 1 hour prior to sexual activity but not more than once daily, during the 12-week treatment period. The initial dose was 50 mg of sildenafil citrate or a medium dose of placebo. Based on the investigator's judgment of efficacy and tolerability, the dose could be increased to 100 mg or decreased to 25 mg of sildenafil citrate or placebo.

Patients were eligible for inclusion in the study if they were aged 18 years or older, had medically documented ED (as defined by the National Institutes of Health Consensus Panel[2]), which was documented in the prior medical record to be of at least 6 months' duration, and a clinical diagnosis (as defined by the National Diabetes Data Group[18]) of at least 5 years duration for type 1 and at least 2 years duration for type 2 diabetes. The diagnosis and etiology classification (ie, organic, psychogenic, or mixed) of ED was based on the patient's medical history, a physical examination, standard laboratory testing, and other diagnostic procedures performed prior to the study. The medical management of patients' diabetes had to be stable for at least 3 months prior to screening, with a hemoglobin A_{1c} value of less than 0.12 and a fasting plasma glucose level of no more than 16.6 mmol/L (300 mg/dL) at screening. The patients also had to be in a stable relationship with a female partner for at least the previous 6 months. Exclusion criteria included the following: penile anatomical deformities that would significantly impair erection; a primary diagnosis of a sexual disorder other than ED; a major psychiatric disorder that was not well controlled with treatment; spinal cord injury; a history of major hematological, renal, or hepatic abnormalities; stroke or myocardial infarction within the previous 6 months; active peptic ulcer; hypotension (a resting blood pressure of <90/50 mm Hg) or hypertension (a resting systolic blood pressure >170 mm Hg or a resting diastolic blood pressure >100 mm Hg); active, proliferative diabetic retinopathy or severe autonomic neuropathy; history of ketoacidosis in the previous 3 years; or regular treatment with nitrates or androgens. Patients were required to discontinue other therapies for ED at screening.

Patients meeting inclusion criteria had their medical histories and demographic information recorded and underwent a full physical examination, which included blood pressure and heart rate measurements, a 12-lead electrocardiogram, and standard biochemistry and hematological laboratory tests. At week 0 (baseline), each eligible patient was given a randomization number using an interactive voice response system, which followed a randomization table generated by the method of random permuted blocks.[19] The investigator provided the patient with study drug in bottles labeled with the corresponding randomization number. The system generating the randomization assignment was geographically and operationally independent from the study investigators who executed the randomization assignment and conducted the study.

Outcome Measures

The efficacy of oral sildenafil was assessed using the self-administered International Index of Erectile Function (IIEF), a 15-question, validated measure of erectile dysfunction,[20] a global efficacy question ("Did the treatment improve your erections?"), and an event log in which patients recorded the number of attempts at sexual intercourse and the number of attempts that were successful. International Index of Erectile Function question 3, which assesses the ability to achieve an erection for sexual intercourse, and question 4, which assesses the ability to

maintain an erection after penetration, specifically address the key aspects of ED as defined by the National Institutes of Health.[2] Responses to these IIEF questions assessed treatment outcomes for the previous 4 weeks and were scored using a 5-point, ordered, categorical scale, with a score of 1 representing the worst response (almost never/never) and a score of 5 representing the best response (almost always/always). Where applicable, a score of 0 indicated no attempts at sexual intercourse. Patients completed the IIEF at week 0 (baseline) and week 12.

All adverse events occurring during treatment or within 7 days of the end of treatment were recorded, regardless of causal relationship to study drug, and standard biochemistry and hematological laboratory tests were conducted at baseline and at 2, 4, 8, and 12 weeks of treatment.

Statistical Analysis

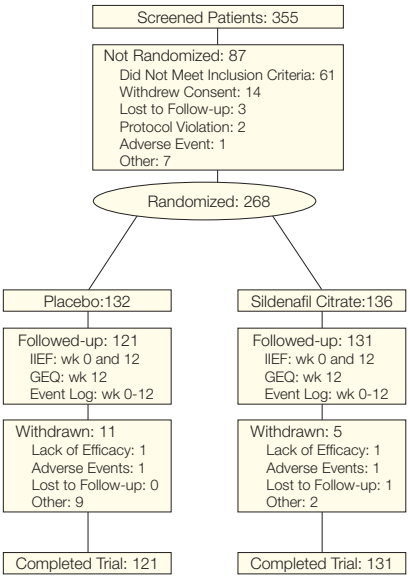
The number of patients required for enrollment in the study was determined by the responses to questions 3 and 4 of the IIEF.[20] The treatment difference between sildenafil and placebo was assumed to be 0.75 and the common variance was assumed to be 2.3. Using these assumptions, a sample size of 86 patients per treatment group would be required to achieve a power of 90%. With a projected patient dropout rate of 25%, the total number of patients required for randomization was determined to be 230 (115 patients for each treatment group).

Least squares mean response scores to the IIEF questions were analyzed using analysis of covariance, which included main-effect terms for treatment, investigational center, and baseline score, with covariates for age, etiology of disease, duration of disease, and smoking status. Responses to the global efficacy question and the proportion of attempts at sexual intercourse that were successful were analyzed using a logistic regression model with the same terms and covariates as mentioned above for the analysis of covariance model. Each subgroup analysis used the same model and terms as the full analysis, omitting the subgroup variable as a covariate when appropriate. Intention-to-treat analyses were performed on all efficacy variables and included all subjects who had a baseline measurement and at least 1 measurement after the start of treatment. All analyses of significance were 2-sided and tested at the 5% level. All patients who received the study drug were included in the safety analysis.

RESULTS

A total of 268 patients were randomized to treatment, with 136 patients receiving sildenafil and 132 patients receiving placebo (FIGURE 1). The baseline characteristics of the patients in the 2 the treatment groups were similar (TABLE 1). The majority of patients had type 2 diabetes, were between the ages of 45 and 64 years, and had had ED for several years. The median length of treatment was 85 days for both the sildenafil and the placebo treatment groups. The median number of doses taken as needed was 31 (range, 3-81) for patients receiving sildenafil and 25 (range, 2-83) for patients receiving placebo. At the end of the study, 126 patients (93%) were receiving 100 mg of sildenafil citrate, 10 patients (7%) were receiving 50 mg of sildenafil citrate, and no patient was receiving 25 mg of sildenafil citrate. For patients receiving placebo, 127 patients (96%), 5 patients (4%), and no patients were taking the high, medium, and low doses, respectively. Of the 268 patients randomized to treatment, 252 (94%) com-

Figure 1. Progress of Patients Throughout the 12-Week Trial



IIEF indicates International Index of Erectile Function; GEQ, general efficacy question. In the placebo group, 5 patients withdrew consent, 3 were withdrawn due to abnormalities in laboratory test results, and 1 was withdrawn for missing a follow-up appointment. Two patients in the sildenafil group withdrew consent.

Table 1. Baseline Demographic Characteristics of Patients With Erectile Dysfunction (ED) and Diabetes

Characteristic	Placebo (n = 132)	Sildenafil Citrate (n = 136)
Mean age, y (range)	57 (27-79)	57 (33-76)
Mean duration of ED, y (range)	5.8 (1-24)	5.3 (0.6-22)
ED etiology, No. (%)*		
Organic	127 (96)	129 (95)
Mixed organic/psychogenic	5 (4)	7 (5)
Mean duration of diabetes, y	12.1	12.1
Type of diabetes, No. (%)		
1	28 (21)	22 (16)
2	104 (79)	114 (84)
Medical history, No. (%)		
Hypertension (past or present)	67 (51)	72 (53)
Ischemic heart disease (past or present)	33 (25)	37 (27)
Concomitant medication, No. (%)		
Antihypertensive agents	71 (54)	70 (54)
Diuretics	19 (14)	14 (10)
β-Blockers	9 (7)	10 (7)
Antidepressant agents	7 (5)	6 (4)

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

pleted the study (131/136 receiving sildenafil and 121/132 receiving placebo).

Efficacy

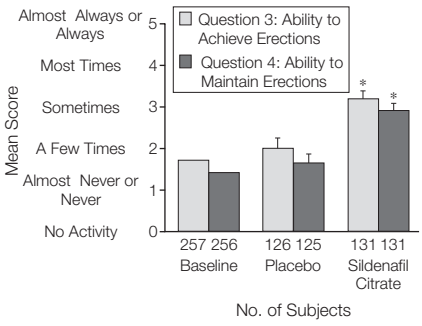
After 12 weeks of treatment, patients receiving sildenafil demonstrated significantly improved erectile function compared with those receiving placebo. The least squares mean scores to the IIEF questions assessing the ability to achieve (question 3) and maintain (question 4) erections demonstrated significant improvements among patients receiving sildenafil compared with those receiving placebo ($P<.001$; FIGURE 2). For question 3, the mean score was 3.2 for patients in the sildenafil group compared with 2.0 for those in the placebo group, which represent increases from baseline of 78% (mean score at baseline, 1.8) and 25% (mean score at baseline, 1.6), respectively. For question 4, the mean score was 2.9 (93% increase from baseline mean score of 1.5) for the sildenafil group compared with 1.6 (14% increase from baseline mean score of 1.4) for the placebo group.

Of the remaining 13 questions of the IIEF, mean scores to 11 questions assessing other aspects of male sexual function, including orgasmic function, satisfaction with sexual intercourse, and overall satisfaction, showed significant improvements for the sildenafil group compared with the placebo group ($P<.001$; TABLE 2). The mean scores for IIEF questions 11 and 12, which assessed frequency of sexual desire and the level of sexual desire, respectively, indicated no statistically significant differences between the 2 groups ($P = .71$ and $P = .17$, respectively).

At the 12-week end point, 74 (56%) of 131 patients taking sildenafil reported improved erections compared with 13 (10%) of 127 patients taking placebo ($P<.001$). Data from patient event logs showed that the proportion of attempts at sexual intercourse that were successful during the last 4 weeks of treatment was significantly greater for all patients (both responders and nonresponders). The proportion of men reporting this was 48% (56/117) in the sildenafil group compared with 12% (14/114) in the placebo group ($P<.001$). The proportion of men with at least 1 successful attempt at intercourse was 61% (71/117) for the sildenafil group vs 22% (25/114) for the placebo group ($P<.001$).

The efficacy of treatment, as assessed with IIEF questions 3 and 4 and the global efficacy question, was also analyzed for various subgroups of patients (TABLE 3). Treatment with sildenafil significantly improved erectile function across all 3 efficacy variables regardless of patient age ($P<.002$ vs placebo), the duration of ED ($P<.001$ vs placebo), and the duration of diabetes ($P<.001$ vs placebo). For patients with type 1 diabetes and those with type 2 diabetes, the baseline mean scores for question 3 of the IIEF were 1.8 and 1.5 for the placebo group and 2.0 and 1.8 for the sildenafil group, respectively ($P = .103$). The baseline mean scores for question 4 for patients with type 1 and type 2 diabetes were 1.2 and 1.3 for the placebo group and 1.7 and 1.5 for the sildenafil group,

Figure 2. Scores on Questions 3 and 4 of the International Index of Erectile Function



Mean (SE) scores at baseline and after 12 weeks of treatment with placebo or sildenafil citrate. Asterisks indicate $P<.001$ vs placebo for treatment effect.

Table 2. Mean Scores to Questions 1, 2, and 5 Through 15 of the International Index of Erectile Function at Baseline and After 12 Weeks of Treatment With Placebo or Sildenafil

	Mean Score						
	Placebo (n = 127)			Sildenafil Citrate (n = 131)			Overall Treatment
Question	Baseline	Final*	*P* Value†	Baseline	Final*	*P* Value†	*P* Value‡
(1) Frequency of erections during sexual activity	1.9	1.8 (0.2)	.11	2.1	3.1 (0.2)	<.001	<.001
(2) Frequency of erections hard enough for penetration	1.6	1.8 (0.2)	.88	1.7	3.1 (0.2)	<.001	<.001
(5) Maintaining erection to completion of intercourse	1.2	1.6 (0.2)	.21	1.4	2.7 (0.2)	<.001	<.001
(6) Frequency of attempts at intercourse	1.9	2.7 (0.2)	<.001	2.0	3.4 (0.2)	<.001	<.001
(7) Frequency of satisfaction with intercourse	1.5	1.7 (0.3)	.32	1.6	2.8 (0.3)	<.001	<.001
(8) Enjoyment of intercourse	1.6	1.8 (0.2)	.63	1.8	2.8 (0.2)	<.001	<.001
(9) Frequency of ejaculation	2.9	3.3 (0.2)	.49	2.9	3.9 (0.2)	<.001	<.001
(10) Frequency of orgasm or climax	2.9	3.3 (0.3)	.47	2.9	3.7 (0.2)	<.001	<.05
(11) Frequency of sexual desire	3.5	3.7 (0.2)	.40	3.7	3.7 (0.2)	.94	.71
(12) Rating of sexual desire	3.3	3.4 (0.1)	.83	3.3	3.5 (0.1)	.08	.17
(13) Satisfaction with sex life	1.7	2.1 (0.2)	.003	1.9	2.9 (0.2)	<.001	<.001
(14) Satisfaction with sexual relationship	2.5	2.8 (0.2)	.02	2.6	3.3 (0.2)	<.001	.001
(15) Rating of confidence in achieving/maintaining erections	1.5	1.6 (0.2)	.06	1.6	2.5 (0.2)	<.001	<.001

*Least squares mean (SE) scores for the last 4 weeks of treatment; scores are based on a scale of 1 to 5, with a higher score indicating a more favorable outcome.[20] For questions 1, 2, and 5 through 10, a score of 0 represented no activity or intercourse.
†*P* values for comparisons between baseline and final scores within each treatment group were calculated using 2-sample *t* test.
‡*P* values for overall treatment effect were calculated using the analysis of covariance model described in the "Methods" section.

respectively ($P = .03$). Each of the 3 efficacy variables demonstrated a significant improvement with sildenafil treatment in patients with type 2 diabetes ($P < .001$ vs placebo). Despite the small number of patients, 2 of the 3 variables were significantly improved with sildenafil treatment in patients with type 1 diabetes ($P < .03$ vs placebo).

Adverse Effects

Of the patients taking sildenafil, 11% reported headache as an adverse event vs 2% of patients taking placebo; 9% taking sildenafil reported dyspepsia vs 0% taking placebo; and 6% taking sildenafil reported respiratory tract disorder (predominantly sinus congestion or drainage) vs 2% taking placebo (TABLE 4). A few patients taking sildenafil experienced flushing, rhinitis, or abnormal vision (predominantly reported as a mild and transient change in brightness perception). The overall incidence of cardiovascular adverse events other than flushing occurred in 3% (4/136) of patients taking sildenafil vs 5% (6/132) of patients taking placebo. In the sildenafil group, 1 patient manifested a Q wave on electrocardiogram with no myocardial infarction documented, 1 patient had congestive heart failure, 1 patient had hypertension, and 1 patient had a varicose vein. In the placebo group, 4 patients had new or worsening chest pain, 1 patient had hypertension, and 1 patient had thrombophlebitis.

Adverse events related to treatment were reported for 16% (22/136) of patients taking sildenafil and 1% (1/132) of patients taking placebo. The majority of adverse events were transient and mild to moderate in nature. No case of priapism was reported. No patient in the sildenafil group discontinued treatment because of a treatment-related adverse event. The rate of discontinuation from treatment was 4% (5/136) of the patients taking sildenafil and 8% (11/132) of patients taking placebo. The reasons for discontinuation of treatment are listed in Figure 1. There were no laboratory test abnormalities attributable to sildenafil use.

COMMENT

Erectile dysfunction, which is a common complication of diabetes, impairs a patient's quality of life, self-esteem, and relationship with his partner.[2] Although psychogenic factors, such as performance anxiety, can contribute to its etiology,[21,22] ED in men with diabetes is predominantly caused by organic factors (ie, vasculogenic and/or neurological abnormalities).[4,5]

Sildenafil is a novel, orally active agent that is an effective and well-tolerated treatment for patients with ED of organic, psychogenic, or mixed etiology.[16] In this study, treatment with sildenafil significantly improved erectile function in men with ED and diabetes. Mean scores for the 2 IIEF questions assessing the ability to achieve and maintain erections indicated significant improvements after treatment with sildenafil compared with mean scores after treatment with placebo. In addition, 56% of patients taking sildenafil reported that treatment had improved their erections compared with only 10% of those taking placebo. The proportion of attempts at sexual intercourse that were successful was 4-fold higher for patients receiving sildenafil than for those receiving placebo. Thus, treatment with sildenafil was shown to be consistently superior to placebo for the efficacy end points evaluated in the study.

The results of the present study support the findings of a placebo-controlled pilot study of 21 diabetic men with ED, which evaluated the efficacy of sildenafil citrate (25 or 50 mg) using penile plethysmography during sexual stimulation, a global efficacy question, and a patient event log.[17] In the pilot study, treatment with sildenafil citrate (50 mg) significantly increased the duration of erections with more than 60% rigidity at the base of the penis compared with placebo. Improved erections were reported by 52% of patients receiving

Table 3. Analysis of Efficacy Variables in Subgroups of Patients With Diabetes After 12 Weeks of Treatment With Placebo or Sildenafil Citrate

Subgroup (No. of Patients*)	Question 3, Mean (SE) Score		Question 4, Mean (SE) Score		GEQ, % Yes	
	Placebo	Sildenafil	Placebo	Sildenafil	Placebo	Sildenafil
Age, y						
18-49 (27; 29)	2.4 (0.6)	3.9 (0.6)†	2.1 (0.6)	3.7 (0.6)†	7	72†
50-64 (70; 62)	2.5 (0.4)	3.3 (0.4)†	1.7 (0.4)	2.8 (0.4)†	11	53†
≥65 (29; 40)	1.4 (0.6)	2.9 (0.6)†	1.4 (0.7)	2.8 (0.6)†	10	50†
Duration of ED, y						
0-3 (36; 51)	3.0 (0.6)	4.3 (0.5)†	1.6 (0.6)	2.9 (0.6)†	11	59†
3-6 (49; 34)	2.2 (0.4)	3.4 (0.5)†	1.7 (0.4)	3.3 (0.4)†	8	65†
>6 (41; 46)	1.3 (0.4)	2.5 (0.4)†	1.6 (0.5)	2.7 (0.5)†	12	48†
Duration of diabetes, y						
0-6 (41; 39)	2.1 (0.5)	3.9 (0.5)†	0.8 (0.5)	2.9 (0.5)†	7	69†
6-12 (40; 39)	1.6 (0.8)	2.4 (0.8)‡	1.5 (0.9)	2.3 (0.8)‡	13	51†
>12 (45; 53)	1.8 (0.4)	2.9 (0.4)†	2.0 (0.4)	3.1 (0.4)†	11	51†
Type of diabetes						
1 (26; 20)	2.1 (0.6)	2.9 (0.7)	1.8 (0.6)	2.8 (0.6)‡	19	55‡
2 (100; 111)	2.1 (0.3)	3.3 (0.3)†	1.7 (0.3)	3.0 (0.3)†	8	57†

*The number of patients in each subgroup is indicated as follows: (placebo group; sildenafil group). ED indicates erectile dysfunction; and GEQ, general efficacy question. Question 3 asks about the ability to achieve erections, and question 4 asks about the ability to maintain an erection.
†$P < .001$ for comparison with placebo using the analysis of covariance model described in the "Methods" section.
‡$P < .05$ for comparison with placebo using the analysis of covariance model described in the "Methods" section.

Table 4. Incidence of Adverse Events*

Adverse Event	Placebo	Sildenafil Citrate
Headache	2 (2)	15 (11)
Dyspepsia	0 (0)	12 (9)
Respiratory tract disorder	2 (2)	8 (6)
Flushing	0 (0)	6 (4)
Rhinitis	0 (0)	5 (4)
Abnormal vision†	1 (1)	5 (4)

*Adverse events of all causes occurring in at least 3% of patients. All data are presented as number (percentage).
†Predominantly a mild and transient change in brightness perception.

sildenafil citrate (50 mg) compared with 10% of those receiving placebo ($P<.05$), and the number of erections sufficiently rigid for penetration increased significantly with sildenafil treatment ($P=.0002$ compared with placebo). In a previously reported study of patients with broad-spectrum ED,[16] the mean final scores for IIEF questions 3 and 4 for patients taking sildenafil citrate (25 -100 mg) were higher than those reported herein for patients with ED and diabetes. However, mean baseline scores for these questions also were somewhat higher in the patients with broad-spectrum ED, suggesting a greater severity of ED in patients with diabetes.

In analyses of various subgroups of patients with ED and diabetes, the efficacy of sildenafil was not affected by patient age, the duration of ED, or the duration of diabetes. Although the present study was not specifically designed to evaluate the subgroup of patients with type 1 diabetes, the results for this subgroup were broadly similar to those for patients with type 2 diabetes. Additional studies with appropriate sample sizes are needed to evaluate the efficacy of sildenafil in patients with type 1 diabetes, diabetes and arterial insufficiency, and diabetes and neuropathy.

Although patients with diabetes frequently are included in placebo-controlled studies evaluating the efficacy of treatments for ED, published articles have not reported treatment outcomes specific to this patient population. However, in a retrospective study of 33 men with ED and diabetes who received intracavernosal injection therapy, Bell and associates[23] reported a response rate of 36% (11 men). Patient age was a predictive factor for a response in this previously reported study; only 1 (7%) of 14 patients with diabetes older than 60 years reported a response to treatment. In the present study, 57% of patients with diabetes and ED reported improved erections with sildenafil treatment. Since different studies use different criteria for defining a response, comparative studies are needed to appropriately assess treatment outcomes with different types of therapies in patients with diabetes and ED.

In this study, treatment with sildenafil was well tolerated. The safety profile of sildenafil in patients with diabetes was reassuring given the chronic complications associated with diabetes. The most common adverse events associated with sildenafil treatment were headache, dyspepsia, and respiratory tract disorder (sinus congestion or drainage), which were predominantly transient and mild or moderate in nature. These adverse events reflect the known pharmacological properties of sildenafil as a PDE5 inhibitor. The incidences of cardiovascular adverse events were comparable in the sildenafil and placebo treatment groups. However, since a degree of risk is associated with sexual activity, physicians should consider the cardiovascular status of their patients prior to initiating any treatment for ED. No patient discontinued treatment with sildenafil due to a treatment-related adverse event, and laboratory test results showed no evidence of abnormalities related to sildenafil treatment.

The exact pathogenesis of ED in men with diabetes remains to be determined. However, advanced glycosylated end products, which accumulate in tissue proteins and play a role in many of the complications of diabetes, have been shown to decrease nitric oxide activity and to modulate endothelium-dependent relaxation, possibly via regulation of penile nitric oxide synthase isozymes.[24] The efficacy of sildenafil, a potent inhibitor of PDE5, in improving erectile function in patients with diabetes suggests that PDE5 activity remains at least partially intact in diabetes. However, studies in animal models of diabetes are needed to confirm or refute this hypothesis.

In summary, the results of this study indicate that oral sildenafil is an effective and well-tolerated treatment for organic ED in men with diabetes.

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