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ORAL SILDENAFIL IN THE TREATMENT OF ERECTILE DYSFUNCTION

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ABSTRACT

Background Sildenafil is a potent inhibitor of cyclic guanosine monophosphate in the corpus cavernosum and therefore increases the penile response to sexual stimulation. We evaluated the efficacy and safety of sildenafil, administered as needed in two sequential double-blind studies of men with erectile dysfunction of organic, psychogenic, or mixed causes.

Methods In a 24-week dose–response study, 532 men were treated with oral sildenafil (25, 50, or 100 mg) or placebo. In a 12-week, flexible dose-escalation study, 329 different men were treated with sildenafil or placebo, with dose escalation to 100 mg based on efficacy and tolerance. After this dose-escalation study, 225 of the 329 men entered a 32-week, open-label extension study. We assessed efficacy according to the International Index of Erectile Function, a patient log, and a global-efficacy question.

Results In the dose–response study, increasing doses of sildenafil were associated with improved erectile function (P values for increases in scores for questions about achieving and maintaining erections were <0.001). For the men receiving 100 mg of sildenafil, the mean score for the question about achieving erections was 100 percent higher after treatment than at base line (4.0 vs. 2.0 of a possible score of 5). In the last four weeks of treatment in the dose-escalation study, 69 percent of all attempts at sexual intercourse were successful for the men receiving sildenafil, as compared with 22 percent for those receiving placebo ($P<0.001$). The mean numbers of successful attempts per month were 5.9 for the men receiving sildenafil and 1.5 for those receiving placebo ($P<0.001$). Headache, flushing, and dyspepsia were the most common adverse effects in the dose-escalation study, occurring in 6 percent to 18 percent of the men. Ninety-two percent of the men completed the 32-week extension study.

Conclusions Oral sildenafil is an effective, well-tolerated treatment for men with erectile dysfunction. (N Engl J Med 1998;338:1397-404.)

ERECTILE dysfunction, the persistent inability to achieve or maintain an erection sufficient for satisfactory sexual performance, is estimated to affect up to 30 million men in the United States.[1] The disorder is age-associated,[1-3] with estimated prevalence rates of 39 percent among men 40 years old and 67 percent among those 70 years old.[2] The available treatments include vacuum-constriction devices; intracavernosal injections of vasoactive agents, including alprostadil (prostaglandin E_1)[4]; transurethral delivery of alprostadil[5]; implantation of penile prostheses; and venous or arterial surgery. No effective oral therapy for erectile dysfunction is currently available.[6]

Normal penile erection depends on the relaxation of smooth muscles in the corpora cavernosa. In response to sexual stimuli, cavernous nerves and endothelial cells release nitric oxide, which stimulates the formation of cyclic guanosine monophosphate (GMP) by guanylate cyclase.[7-9] The mechanism by which cyclic GMP stimulates relaxation of the smooth muscles remains to be elucidated. Sildenafil is a selective inhibitor of cyclic-GMP–specific phosphodiesterase type 5, the predominant isozyme metabolizing cyclic GMP in the corpus cavernosum.[10] By selectively inhibiting cyclic-GMP catabolism in cavernosal smooth-muscle cells,[11] sildenafil would be expected to restore the natural erectile response to sexual stimulation but not

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cause erections in the absence of such stimulation. Sildenafil is rapidly absorbed, with maximal plasma concentrations occurring within one hour after oral administration and a mean terminal half-life of three to five hours.[10] In a placebo-controlled pilot study of 12 men, sildenafil significantly improved the erectile response during visual sexual stimulation.[10,12] We therefore undertook two studies to evaluate in a home setting the efficacy and safety of sildenafil in men with erectile dysfunction.

METHODS

In two sequential studies, we studied a total of 861 men 18 years of age or older with a clinical diagnosis of erectile dysfunction (as defined previously[1]) of six months' duration or longer at 37 centers in the United States. Each man had to be in a stable relationship with a female partner that had begun at least six months earlier. The cause of erectile dysfunction was determined from the medical history, physical examination, and other diagnostic procedures, including a test involving the intracavernosal injection of a vasoactive drug (done in 31 percent of the men), a RigiScan test of nocturnal penile tumescence (26 percent), penile duplex ultrasonography (21 percent), and endocrine testing (21 percent). On the basis of these evaluations, the men were classified as having organic, psychogenic, or mixed erectile dysfunction. Of the 861 men studied, 605 (70 percent) were judged to have organic erectile dysfunction, 99 (11 percent) to have psychogenic erectile dysfunction, and 157 (18 percent) to have mixed erectile dysfunction. Men were excluded if they had penile anatomical defects, a primary diagnosis of another sexual disorder (e.g., premature ejaculation), spinal cord injury, any major psychiatric disorder not well controlled with treatment, poorly controlled diabetes mellitus, active peptic ulcer disease, a history of alcohol or substance abuse, major hematologic, renal, or hepatic abnormalities, or a recent (within the previous six months) stroke or myocardial infarction or if they were receiving nitrate therapy. Other erectile-dysfunction therapies were discontinued at the time of screening (four weeks before the subjects received the study medication). Sildenafil (Viagra) and an identical-looking placebo were supplied by Pfizer. The men were instructed to take a dose approximately one hour before planned sexual activity but not more than once daily. The protocols were approved by the institutional review board at each center, and all the men gave written informed consent.

We assessed efficacy by using the responses to question 3 (frequency of penetration) and question 4 (maintenance of erections after penetration) of the 15-question International Index of Erectile Function, a validated, multidimensional, self-administered questionnaire used for the clinical assessment of erectile dysfunction and treatment outcomes in clinical studies.[11] The responses to these two questions pertaining to the ability to achieve and maintain an erection sufficient for sexual intercourse, as described in the definition of erectile dysfunction,[1] were rated on a scale of 1 (almost never or never) to 5 (almost always or always). A score of 0 indicated no attempt at sexual intercourse. The mean score for each of the two questions was 4.3 for 109 normal men, 31 to 86 years old, with an age distribution similar to that of the men with erectile dysfunction (unpublished data). Efficacy was also assessed on the basis of the scores for the five separate response domains of male sexual function of the International Index[13]: erectile function (questions 1 through 5 and 15; possible total score, 1 to 30); orgasmic function (questions 9 and 10; possible total score, 0 to 10); sexual desire (questions 11 and 12; possible total score, 2 to 10); intercourse satisfaction (questions 6, 7, and 8; possible total score, 0 to 15); and overall satisfaction (questions 13 and 14; possible total score, 2 to 10). The domain scores were computed by adding the scores for the individual questions in each domain. Other means of assessing efficacy were an event log, in which we asked the men to record the date and dose of medication taken, the presence of sexual stimulation, the hardness of erections (graded on a four-point scale), and whether sexual intercourse was successful, and a global-efficacy question ("Did the treatment improve your erections?"), with a response of yes or no. The end points of the International Index quantified the magnitude of the response, and the global-efficacy question and the event log provided qualitative assessments of efficacy. Physical examinations and standard blood-chemistry and hematologic laboratory tests were performed throughout the studies. Adverse effects were recorded by the investigators.

Study of Dose–Response, Efficacy, and Safety

In this double-blind, placebo-controlled, fixed-dose study, 532 men were randomly assigned to take placebo or 25, 50, or 100 mg of sildenafil (approximately one hour before planned sexual activity but not more than once daily) for 24 weeks. Each dose consisted of three tablets from the same row of a blister pack (placebo–placebo–placebo; placebo–placebo–25 mg; placebo–placebo–50 mg; or placebo–50 mg–50 mg). The men were instructed not to consume more than two alcoholic drinks within one hour of sexual activity. Each man completed the International Index of Erectile Function at 0, 12, and 24 weeks and was asked about global efficacy at 12 and 24 weeks. The event logs were reviewed at 0, 2, 4, 8, 12, 16, 20, and 24 weeks.

Study of Flexible Dose Escalation, Efficacy, and Safety with a Long-Term, Open-Label Extension

In the flexible dose-escalation study, 329 different men were randomly assigned to take placebo or 50 mg of sildenafil approximately one hour before sexual activity for 12 weeks. At each follow-up visit, the dose could be doubled or reduced by 50 percent on the basis of the therapeutic response and adverse effects. Each man completed the International Index of Erectile Function at 0 and 12 weeks and was asked about global efficacy at week 12. The event logs were reviewed at 0, 2, 4, 8, and 12 weeks. The men who completed the study and who did not have any serious adverse effects were eligible to receive open-label sildenafil for an additional 32 weeks.

Statistical Analysis

The mean frequency of responses to questions 3 and 4 of the International Index of Erectile Function for each treatment group was calculated. An analysis-of-covariance model was fitted for each question, which included main-effect terms for investigational center and treatment effect (as ordered categorical variables), with base-line score, patient age, smoking, and duration and cause of erectile dysfunction as covariates. Mean domain scores from the International Index were calculated, and the treatment effect was analyzed by using the analysis-of-covariance model described above. From the event log, the mean numbers of grade 3 and grade 4 erections (in the dose–response study) or the percentage of attempts at sexual intercourse that were successful (in the dose-escalation study) was calculated. Analysis of covariance (dose–response study), with adjustment for the covariates listed above, or a chi-square test (dose-escalation study) was used to determine the association between the treatment groups. The answers of each treatment group to the global-efficacy question (yes or no) were analyzed with the use of logistic-regression analysis, accounting for the same covariates as those listed for the analysis-of-covariance models. Intention-to-treat analyses were performed on all variables and included all the men who were randomly assigned to treatment (and received treatment) and who had any assessments after base line, regardless of protocol deviations or whether the men completed the study. All statistical tests were two-sided.

TABLE 1. BASE-LINE CHARACTERISTICS OF THE MEN WITH ERECTILE DYSFUNCTION TREATED WITH SILDENAFIL OR PLACEBO IN TWO STUDIES.

CHARACTERISTIC	DOSE–RESPONSE STUDY		DOSE-ESCALATION STUDY	
	PLACEBO (N=216)	SILDENAFIL (N=316)	PLACEBO (N=166)	SILDENAFIL (N=163)
Age (yr)				
Mean	57	58	59	60
Range	20–79	24–87	31–81	26–79
Mean duration of erectile dysfunction (yr)	3.2	3.2	4.7	5.0
Cause of erectile dysfunction (% of men)*				
Organic	77	78	63	55
Psychogenic	10	9	16	14
Mixed	13	13	22	31
Concomitant condition (% of men)				
Hypertension	26	30	28	24
Ischemic heart disease (past or present)	8	8	8	15
Hyperlipidemia	16	19	14	15
History of radical prostatectomy	10	12	11	9
Diabetes mellitus	15	13	11	8

*The cause of erectile dysfunction was determined by the investigators on the basis of the history, physical examination, and additional diagnostic studies (see the Methods section). Because of rounding, percentages do not always total 100.

RESULTS

The base-line characteristics of the men with erectile dysfunction enrolled in each study were similar, but there were differences between the studies (Table 1). The men in the dose–response study had had erectile dysfunction for longer periods, and fewer of them had organic erectile dysfunction. Among the 532 men in the dose–response study, 465 (87 percent) completed the 24-week study (285 of 316 in the sildenafil group and 180 of 216 in the placebo group). Among the 329 men in the dose-escalation study, 307 (93 percent) completed the 12-week study (154 of 163 in the sildenafil group and 153 of 166 in the placebo group).

After 12 weeks of treatment in the dose-escalation study, the proportions of men taking 25, 50, or 100 mg of sildenafil were 2 percent (4 men), 23 percent (38 men), and 74 percent (121 men), respectively. For the men taking placebo, the corresponding proportions were 0 percent, 5 percent (8 men), and 95 percent (158 men). Two hundred twenty-five men who completed the 12-week study were enrolled to receive open-label sildenafil for an additional 32 weeks.

Efficacy

In the dose–response study, increasing doses of sildenafil were associated with higher mean scores for the questions of the International Index of Erectile Function assessing frequency of penetration (question 3) and maintenance of erections after sexual penetration (question 4) ($P<0.001$) (Table 2). The mean scores for these questions did not vary according to the cause of erectile dysfunction. For question 3, the percentage increases in mean score from base line to the end of treatment were 60, 84, and 100 percent for the men who received 25, 50, and 100 mg of sildenafil, respectively, as compared with an increase of 5 percent for the men who received placebo. For question 4, the corresponding values were 121, 133, and 130 percent for the men who received 25, 50, and 100 mg of sildenafil, respectively, as compared with 24 percent for those who received placebo.

In the dose-escalation study, the mean scores for questions 3 and 4 of the International Index were significantly higher after treatment for the sildenafil group than for the placebo group ($P<0.001$) (Table 2). The percent increase from base line was 95 percent for question 3 and 140 percent for question 4 for the men taking sildenafil, as compared with 10 percent and 13 percent, respectively, for those taking placebo.

The mean scores for the erectile-function domain on the International Index increased with increasing doses of sildenafil in the dose–response study ($P<0.001$). The mean score for the erectile-function domain in the dose-escalation study was significantly higher for the men taking sildenafil (22.1) than for those taking placebo (12.2, $P<0.001$) (Fig. 1A). The mean scores for the orgasmic-function, intercourse-satisfaction, and overall-satisfaction domains were also significantly higher in the sildenafil group ($P<0.001$) (Fig. 1B), whereas the mean scores for sexual desire were not significantly different in the two groups ($P=0.13$).

The event-log data on the proportion of men

Table 2. Mean Scores of Responses to Question 3 and Question 4 of the International Index of Erectile Function for the Men Receiving Sildenafil or Placebo in Two Studies.*

Treatment Group	Base-Line Score†	Final Score†	Percent Change from Base Line‡	P Value§
Question 3				
Dose–response				
Placebo (n=199)	2.1±0.1	2.2±0.2	5	
Sildenafil				<0.001
25 mg (n=96)	2.0±0.2	3.2±0.2	60	
50 mg (n=105)	1.9±0.2	3.5±0.2	84	
100 mg (n=101)	2.0±0.2	4.0±0.2	100	
Dose escalation				
All the men				
Placebo (n=138)	2.1±0.1	2.3±0.1	10	
Sildenafil (n=138)	2.0±0.1	3.9±0.1	95	<0.001
Organic cause				
Placebo (n=90)	2.0±0.2	2.0±0.2	0	
Sildenafil (n=81)	1.8±0.2	3.6±0.2	100	<0.001
Psychogenic cause				
Placebo (n=24)	2.2±0.2	2.3±0.4	5	
Sildenafil (n=19)	2.0±0.2	4.3±0.4	115	<0.001
Mixed cause				
Placebo (n=24)	2.3±0.3	2.8±0.3	22	
Sildenafil (n=38)	2.3±0.3	3.6±0.3	57	0.08
Question 4				
Dose–response				
Placebo (n=199)	1.7±0.1	2.1±0.2	24	
Sildenafil				<0.001
25 mg (n=96)	1.4±0.1	3.1±0.2	121	
50 mg (n=105)	1.5±0.1	3.5±0.2	133	
100 mg (n=101)	1.7±0.1	3.9±0.2	130	
Dose escalation				
All the men				
Placebo (n=138)	1.6±0.1	1.8±0.1	13	
Sildenafil (n=137)	1.5±0.1	3.6±0.1	140	<0.001
Organic cause				
Placebo (n=90)	1.4±0.1	1.4±0.2	0	
Sildenafil (n=80)	1.4±0.1	3.3±0.2	136	<0.001
Psychogenic cause				
Placebo (n=24)	1.7±0.2	1.9±0.3	12	
Sildenafil (n=19)	1.6±0.2	3.8±0.4	138	<0.001
Mixed cause				
Placebo (n=24)	1.8±0.3	2.3±0.4	28	
Sildenafil (n=38)	1.6±0.2	3.7±0.4	131	0.005

*Question 3 of the International Index of Erectile Function is, "When you attempted sexual intercourse, how often were you able to penetrate your partner?" Question 4 is, "During sexual intercourse, how often were you able to maintain your erection after you had penetrated your partner?" The analysis was by intention to treat.

†Scores are based on a scale of 1 (almost never or never) to 5 (almost always or always), with 0 representing "did not attempt intercourse." Values are means ±SE.

‡Percent differences are between the final (end-of-treatment) mean scores and the base-line mean scores.

§P values are calculated according to analysis of covariance (ordered categorical variable), with base-line score, patient's age, smoking, and duration and cause of erectile dysfunction as covariates.

achieving erections hard enough for sexual intercourse (i.e., grade 3 or 4) during the last four weeks of treatment showed a significant dose–response relation for sildenafil (72 percent, 80 percent, and 85 percent for doses of 25 mg, 50 mg, and 100 mg, respectively, as compared with 50 percent for placebo; $P<0.001$). The mean number of grade 3 and grade 4 erections and the mean number of grade 4 erections during the last four weeks of treatment were also significantly higher in the sildenafil group ($P<0.001$) (Fig. 2A), with 80 percent of the grade 3 erections and 94 percent of the grade 4 erections resulting in successful sexual intercourse. In the dose-escalation study, 69 percent of all attempts at sexual intercourse by the men receiving sildenafil were successful in the last four weeks of treatment, as compared with 22 percent for those receiving placebo ($P<0.001$) (Fig. 2B). During the last four weeks of treatment, the mean numbers of attempts at sexual intercourse that were successful were 5.9 for men in the sildenafil group and 1.5 for men in the placebo group ($P<0.001$) (Fig. 2B).

After 24 weeks of treatment in the dose–response study, improved erections were reported by 56, 77, and 84 percent of the men taking 25, 50, and 100 mg of sildenafil, respectively, as compared with 25 percent of those taking placebo ($P<0.001$ for treatment effect). After 12 weeks of treatment in the dose-escalation study, 101 of the 136 men in the sildenafil group who responded to the global-efficacy question (74 percent) reported improved erections, as compared with 23 of the 118 men in the placebo group who responded to the question (19 percent, $P<0.001$).

Cessation and Adverse Effects of Treatment

During the dose–response study, 31 of the 316 men in the sildenafil group (10 percent) and 36 of the 216 men in the placebo group (17 percent) discontinued treatment (Table 3). Four men (1 percent) in the sildenafil group stopped taking the drug because of treatment-related adverse effects (nausea and vomiting in one, leg pain and backache in one, intermittent headache and dyspepsia in one, and headache in one), as compared with one man (<1 percent) who stopped taking placebo (because of headache and nausea). Five men (2 percent) in the sildenafil group and 11 men (5 percent) in the placebo group discontinued treatment because of insufficient responses. In the dose-escalation study, 9 men (6 percent) stopped taking sildenafil and 13 men (8 percent) stopped taking placebo. One man stopped taking sildenafil because of treatment-related headache and flushing, and one man stopped because of an insufficient response. Laboratory-test results indicated no evidence of sildenafil-induced abnormalities.

The most frequently reported adverse effects of

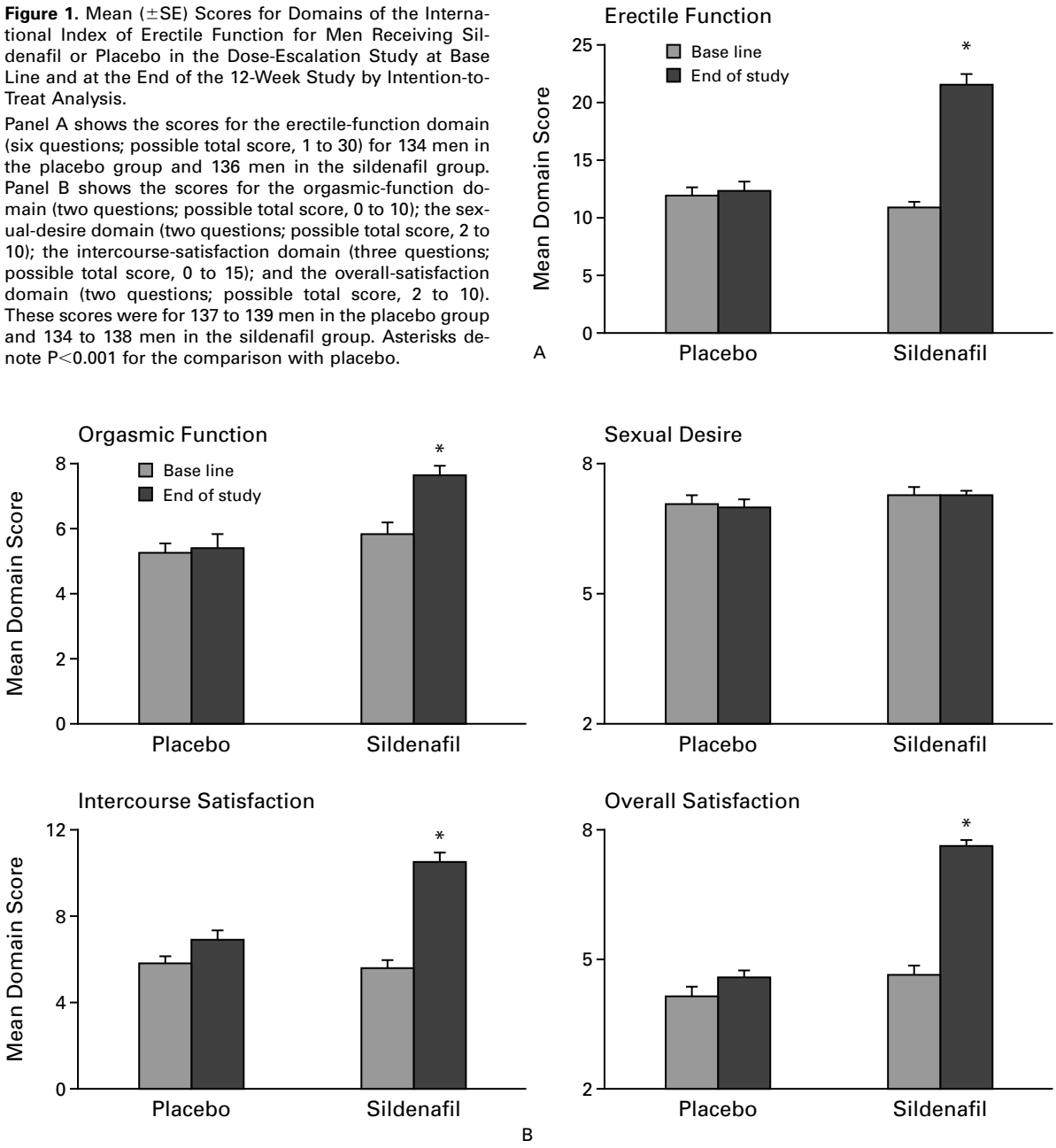

Figure 1. Mean (±SE) Scores for Domains of the International Index of Erectile Function for Men Receiving Sildenafil or Placebo in the Dose-Escalation Study at Base Line and at the End of the 12-Week Study by Intention-to-Treat Analysis.

Panel A shows the scores for the erectile-function domain (six questions; possible total score, 1 to 30) for 134 men in the placebo group and 136 men in the sildenafil group. Panel B shows the scores for the orgasmic-function domain (two questions; possible total score, 0 to 10); the sexual-desire domain (two questions; possible total score, 2 to 10); the intercourse-satisfaction domain (three questions; possible total score, 0 to 15); and the overall-satisfaction domain (two questions; possible total score, 2 to 10). These scores were for 137 to 139 men in the placebo group and 134 to 138 men in the sildenafil group. Asterisks denote $P<0.001$ for the comparison with placebo.

sildenafil in the two studies were transient headache, flushing, dyspepsia, and rhinitis (Table 3). Transient visual disturbances (i.e., changes in the perception of color hue or brightness) were reported by some men. The frequency of these adverse effects increased with increasing doses of sildenafil, but the symptoms were usually mild and lasted a few minutes to a few hours after dosing. No man reported priapism during the studies.

Of the 225 men enrolled in the open-label extension study, 207 (92 percent) completed an additional 32 weeks of sildenafil treatment. Four men (2 percent) withdrew because of treatment-related adverse effects (headache in two, intermittent flushing and blurred vision in one, and groin pain and headache in one).

DISCUSSION

We found that sildenafil improves sexual function in men with erectile dysfunction. In keeping with

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