TREATMENT OF ERECTILE DYSFUNCTION WITH SILDENAFIL

LEONARD S. MARKS, CATHERINE DUDA, FREDERICK J. DOREY, MARIA LUZ MACAIRAN,
AND PAUL BRYAN SANTOS

ABSTRACT

Objectives. To determine the efficacy of sildenafil for the treatment of erectile dysfunction (ED) in a clinical practice setting; to evaluate the correlation between patient and partner perceptions of treatment outcomes; and to assess the relation between the severity of ED and response to treatment.

Methods. Among the first 100 men to receive sildenafil in a urology practice setting, 74 (mean $\pm$ SD age 64 ± 11 years) completed a validated sexual function questionnaire (International Index of Erectile Function [IIEF]) before and after a 4 to 6-week treatment period. A modified version of the same questionnaire was independently completed by partners. ED was categorized into a severity class of I to IV.

Results. Sildenafil treatment improved erections by 71% to 95%, according to responses in key IIEF questions 3 and 4. Overall, 57 (77%) of 74 patients desired to continue treatment after the test period. Patient score on the IIEF was correlated with partner score on the modified questionnaire before and after treatment ($r = 0.67$ to 0.81, $P < 0.01$). IIEF scores were reflected in a simple severity classification system. Men with the best preservation of erections (severity class I) exhibited the best responses to sildenafil, whereas men with no erections (severity class IV) were much less likely to respond to the drug and desire continuation of treatment ($P < 0.01$). Patients with a radical prostatectomy were relatively refractory to sildenafil, except for 2 of 5 who had undergone a nerve-sparing operation.

Conclusions. In clinical practice, sildenafil is an effective treatment of ED, according to partner-validated questionnaire responses; and the results of treatment are predictable with an ED severity classification system.   UROLOGY **53**: 19–24, 1999. © 1999, Elsevier Science Inc. All rights reserved.

Sildenafil citrate is the first oral agent approved by the U.S. Food and Drug Administration for the treatment of erectile dysfunction (ED). From approval on March 27 through August 7, 1998, more than 3.8 million prescriptions were written for more than 2.5 million men, totaling more than 31 million doses (Pfizer Marketing Division, unpublished data). The efficacy and safety of sildenafil have been reported in a large-scale, placebo-controlled clinical trial in which selection of study participants was subject to rigorous inclusion and exclusion criteria.[1] However, scientific reports of usage outside of clinical trials (ie, in the general population of men seeking treatment for ED) are not yet available. We therefore conducted a study of sildenafil usage among the first men to seek this treatment after drug approval.

MATERIAL AND METHODS

PATIENT SCREENING AND PRETREATMENT EVALUATIONS

This was a prospective cohort study. The study included the first 100 men who elected to receive sildenafil therapy for the treatment of ED at a metropolitan Los Angeles urology practice, who met the study inclusion criteria, and who agreed to participate in a short-term, open-label, noncomparative trial (4 to 6 weeks in duration). Inclusion criteria were (1) a history of ED, as defined by the National Institutes of Health (NIH) Consensus Development Panel on Impotence,[2] of at least 1 year in duration; (2) at least a 10th grade education; (3) participation in a discussion of therapeutic options, including the known therapeutic effects and side effects of sildenafil as detailed in the package insert; (4) the ability and willingness of patients and, wherever possible, partners to complete questionnaires; and (5) a willingness to return for a follow-up visit after 4 to 6 weeks of treatment. Exclusion criteria were (1) concomitant use of organic nitrates or nitric oxide donors; (2) alcohol or drug dependence; or (3) major, concurrent, uncontrolled medical illness.

Before treatment, all study participants underwent a detailed medical examination that included information about

the severity of and previous treatments for ED. Previous ED therapies used by these patients included intraurethral alprostadil (45%), intracavernosal injections (39%), and vacuum devices (14%); 35% had received no previous ED treatment. Patients also underwent a routine physical examination, including urinalysis, complete blood count, and multiphasic serum testing before receiving sildenafil.

The present report focuses on the 74 men who completed questionnaires (see Evaluations, below) both before and after treatment. Of the 74 men with complete questionnaires, partner questionnaires were available before treatment in 34 and after treatment in 31. No attempt was made to interview the partners.

DOSAGE AND ADMINISTRATION

Patients meeting the entry criteria were given a prescription for eight 50-mg tablets of sildenafil (n = 47) or received eight 50-mg sample tablets (n = 27), if cost was a potential barrier to study participation. Each patient was instructed to take one 50-mg tablet approximately 1 hour before planned sexual activity and, if displeased with resulting efficacy, to take two tablets at next activity. Patients were instructed to take sildenafil only once within a 24-hour period. The mechanism of action and potential side effects of sildenafil were explained, and a package insert was given to each patient. A follow-up visit was scheduled for 4 to 6 weeks later. Additional drug was made available to each patient as needed.

EVALUATIONS

Efficacy was assessed using the International Index of Erectile Function (IIEF), a 15-item, self-administered questionnaire.[3] The maximum total IIEF score is 75, and the minimum IIEF score is 5, with higher scores indicating greater erectile function. The 15 questions of the IIEF can be grouped into five response domains that address key elements of sexual dysfunction: erectile function, orgasmic function, sexual desire, intercourse satisfaction, and overall satisfaction. Patients completed the IIEF at the start of the study (baseline visit) and again at the follow-up visit. Modified versions of the IIEF questionnaire, along with a stamped, self-addressed envelope, were given to the patient for his partner to complete independently (ie, without patient consultation) at baseline and at the end of the study. Modifications of the questionnaire for the partner were minor; each of the original 15 questions was simply rephrased, asking the partner to evaluate the patient for that item (eg, question 1, "How often was your partner able to get an erection during sexual activity?").

Patients were queried at follow-up regarding their usage of the drug, side effects, and desire to continue treatment.

STATISTICS

Scores for the IIEF before and after treatment were compared using the paired t test and the nonparametric sign rank test. Multivariate linear regression analysis was used to determine the relation between the pretreatment variables and the total outcome and domain scores. Statistical significance was chosen a priori to be $P < 0.05$.

RESULTS

Of the first 100 patients electing to receive sildenafil, 74 completed the IIEF questionnaire both at baseline and at the follow-up visit. A summary of their baseline characteristics is shown in Table I. The mean ± SD age was 64 ± 11 years (range 29 to 80). The majority of patients (82%) had a history of concomitant medical conditions often associated

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TABLE I. *Characteristics of 74 men at baseline*

Age (yr)	
Mean ± SD	64 ± 11
Range	29–80
Race	
White	50
African American	18
Hispanic	4
Asian	2
Marital status	
Married	45
Single	29
Concomitant conditions*	
Hypertension	35%
Coronary artery disease	30%
Radical prostatectomy†	14%
Diabetes mellitus	10%
None	18%
Severity class	
I (satisfactory penetration possible)	14
II (marginal penetration possible)	30
III (partial erections, no penetration)	19
IV (no erections)	11

* Percentages do not total 100% because of comorbidity; only the more common conditions are shown.
† Average interval of 35 ± 29 months (range 6 to 109) between operation and start of sildenafil treatment.
Data presented are number or percent of patients, unless otherwise indicated.

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with erectile dysfunction. Over the 4- to 6-week period, the mean number of tablets taken per patient was 4.5 ± 2.6. At the end of the study, 50 patients (68%) were still taking the recommended 50-mg starting dose, and 24 (32%) had increased the dosage to 100 mg.

Mean responses to questions of the IIEF are shown in Table II. Scores on key questions 3 and 4, which address aspects of the NIH definition of ED and are relevant to the ability to achieve and maintain an erection sufficient for sexual activity, were at the follow-up visit 71% and 95% greater than baseline scores ($P < 0.01$). When items of the IIEF were grouped into sexual domains, mean IIEF scores at the follow-up visit were significantly greater than those at the baseline visit for all domains (all $P < 0.01$). The greatest improvement from baseline was demonstrated in the domain comprising erectile function (66%), and the least improvement was in sexual desire (13%).

Specifically, the ability to resume intercourse was substantial for the entire group. However, this ability was inversely related to ED severity before treatment. On the key questions, penetration/maintenance was improved with sildenafil to a response level of 4 or 5 ("success most times") in 35% to 44% of men who before treatment were at level 0 or 1 ("no attempts or almost never successful") and in 78% to 80% of men who were at level 2

TABLE II. *Patient responses from IIEF questionnaire*

Domain*	Baseline Score (mean ± SD)	Follow-up Score (mean ± SD)	Change	P Value
Erectile function	12.5 ± 7.2	20.7 ± 9.6	66%	<0.01
Question 3†	2.0 ± 1.5	3.4 ± 1.8	71%	<0.01
Question 4‡	1.7 ± 1.4	3.4 ± 1.9	95%	<0.01
Orgasmic function	5.7 ± 3.3	7.3 ± 3.4	27%	<0.01
Sexual desire	6.5 ± 1.9	7.3 ± 2.2	13%	<0.02
Intercourse satisfaction	6.8 ± 3.7	9.8 ± 4.1	44%	<0.01
Overall satisfaction	5.4 ± 2.7	7.5 ± 2.7	39%	<0.01

KEY: IIEF = International Index of Erectile Function
* Erectile function (possible total score 1 to 30); orgasmic function (possible total score 0 to 10); sexual desire (possible total score 2 to 10); intercourse satisfaction (possible total score 0 to 15); and overall satisfaction (possible total score 2 to 10).
† "When you attempted sexual intercourse, how often were you able to penetrate (enter) your partner?" Rated on a scale of 1 (almost never or never) to 5 (almost always or always); score of 0 = no attempts made.
‡ "During sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner?" Rated on a scale of 1 (almost never or never) to 5 (almost always or always); score of 0 = no attempts made.
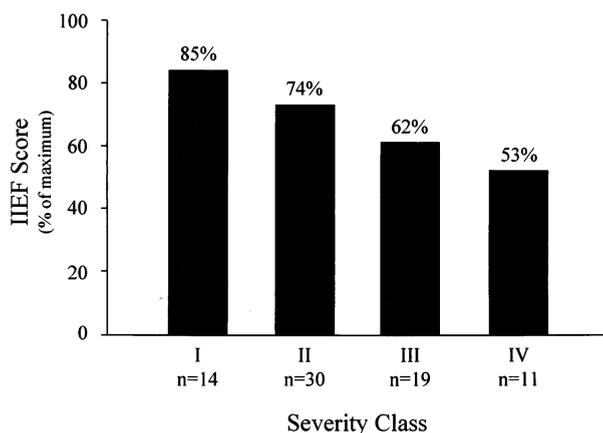

FIGURE 1. *Relation between total IIEF score, denoted as percent of maximum score (75) (vertical axis) and severity class (horizontal axis) is shown for the 74 men at baseline. I = satisfactory penetration possible (n = 14); II = marginal penetration possible (n = 30); III = partial erections/no penetration (n = 19); IV = no erections (n = 11).*

or 3 ("success at half or less than half the times"). Regarding resumption of successful intercourse with sildenafil, the less impaired men significantly outperformed the more severely impaired men ($P <0.01$). Of the 30 men who were unable to achieve penetration, 13 were able to do so with the drug.

In Figure 1 the inverse relation between total IIEF score and severity class at baseline is shown for the 74 men completing all questionnaires. The higher the severity class, the lower the IIEF score. For example, men in severity class I (ie, capable of satisfactory penetration) reported an IIEF score averaging 85% of maximum, which is 75. At the other extreme, men with class IV severity (ie, no erec-

tions) reported total IIEF scores that were on average only 53% of the maximum possible IIEF score. The relation between the IIEF total score and severity class was statistically significant ($P <0.01$).

In Table III, the relation is shown between severity class and patient responses on the key IIEF questions 3 and 4 for the men with the lowest questionnaire scores (0 to 1). As seen in Table III, the higher the severity class, the greater the percentage of men with very low scores on the questionnaires. In a corresponding analysis, men with the highest questionnaire scores were found to have a low severity class. The two measures—one based on a patient's written response to a question and the other based on a physician's impression during an interview—were correlated ($P <0.01, r = -0.53$ to -0.48).

In Figure 2, the outcome variable, "Do you wish to continue sildenafil?" (vertical axis), is related to the patient's severity class at baseline (horizontal axis) for the 74 men with complete questionnaires. The higher the severity class, the less likely the patient would be to desire to continue treatment: 93% of class I patients, but only 55% of class IV patients, wanted to continue sildenafil. Stated differently, men capable of some penetration before treatment were almost twice as likely to desire continuation of sildenafil as men not capable of any erection before treatment. Overall, 57 (77%) of the 74 men elected to continue sildenafil after their initial trial. Of the 17 men electing not to continue, only 2 discontinued because of bothersome side effects (see below).

Modified IIEF questionnaires were completed by 34 partners at baseline and 31 after treatment. As shown in Figure 3, for both baseline and post-treatment evaluations, patient and partner assessment

TABLE III. *Percent of men with a score of 0 or 1 (severe impairment) on key IIEF questions grouped by severity class* *

IIEF Question[†]	Severity Class			
	I	II	III	IV
3	14 (2/14)	30 (9/30)	68 (13/19)	91 (10/11)
4	21 (3/14)	40 (12/30)	74 (14/19)	91 (10/11)

KEY: *Abbreviations as in Table II.*
* *Severity classes as in Table I.*
[†] *IIEF Questions 3 and 4 as in Table II.*
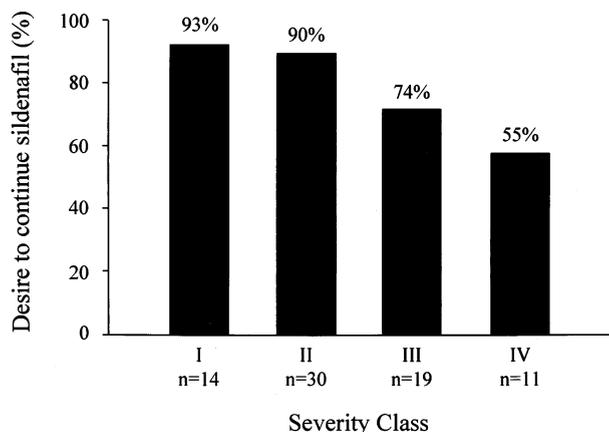*Numbers shown are percentage (IIEF/severity).*

FIGURE 2. *Relation between the patient's desire to continue sildenafil therapy (vertical axis) and baseline severity class (horizontal axis). The more severe the dysfunction, the less likely the patient's desire to continue sildenafil therapy.*

were correlated ($r = 0.67$ to 0.81, $P < 0.01$). In other words, judging by IIEF total scores, a statistically significant association was found between patient and partner perceptions of the patient's sexual function. When key questions 3 or 4 were analyzed separately, similar correlations were found.

Among the 14 men who had undergone radical prostatectomy, results of sildenafil therapy were substantially worse than in the other men. Most of these men were in severity class IV (ie, having no erections), and none of these postoperative class IV patients were satisfied with sildenafil treatment. Nerve-sparing surgery had been performed in 5 of the 14 patients, and 2 of them, both capable of penetration without therapy, exhibited further symptomatic improvement and elected to continue receiving treatment. Sildenafil therapy failed in the other 12 postoperative patients, and they chose not to continue it as a long-term treatment option.

A principal, bothersome side effect of sildenafil was identified as follows by 16 (22%) of the 74 patients: headache (n = 5), flushing (n = 5), nasal congestion (n = 3), dyspepsia (n = 1), pain in left arm (n = 1), and blue vision (n = 1). Two patients

discontinued treatment because of bothersome side effects, 1 with headache and 1 with flushing. Otherwise, reported side effects were mild and transitory and did not interfere with treatment. No priapism and no deaths were encountered.

Whether the patient received free samples (n = 27) or not (n = 47), outcomes were essentially the same. Baseline IIEF scores were approximately the same in the two groups (total score 51 to 53). On completion of the study, "desire to continue sildenafil" was 73% in the free-sample group and 82% in the other (P = NS).

COMMENT

The advent of sildenafil has dramatically changed treatment of male ED. "Not surprisingly, patients are clamouring for the drug,"[4] and, as noted earlier, physicians are responding positively to the demand. The safety and efficacy of sildenafil have been convincingly demonstrated in a large, rigorously controlled clinical trial.[1] However, as with other treatments, major differences have been noted between results obtained in a clinical trial and those seen in a clinical practice setting. For example, in clinical trials, transurethral alprostadil was found to allow intercourse in 70% of men with ED,[5] but in a clinical practice setting, the success rate was found to be only 37%.[6]

In the present study, differing considerably from a controlled trial, we found that sildenafil usage enhanced erectile function in a practice setting. Patients studied here were on average approximately 5 years older, had more concomitant disease, were less inclined to take the 100-mg dose, and were more often lacking a stable partner than men in the trial. In addition, the present group had a great deal more information about the product: the package insert—not available during the trial—was reviewed with each patient and a copy given to him on drug administration. Despite the above differences, the practice results approximated the trial outcomes. Using key questions 3 and 4 from the IIEF, erectile function was improved by 71% to 95% in the present group and
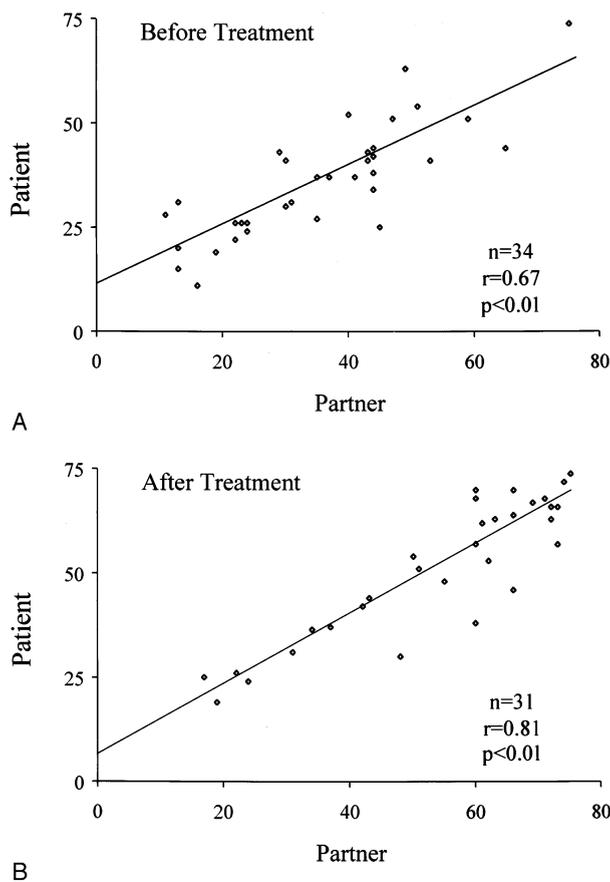
FIGURE 3. *Scattergrams showing relation between responses of patient (vertical axis) and partner (horizontal axis) on IIEF total score before (A) and after (B) sildenafil treatment. Patient and partner assessments of erectile function are directly correlated.*

overall. Overall, 77% of the men elected to continue using sildenafil after completion of the study period; although "desire to continue sildenafil" does not prove drug efficacy, it must approximate such an outcome, especially because all continuing men in this study would then be paying for the product.

An ED severity class was found to reflect the more complicated IIEF total score and appeared helpful in predicting treatment response. Although not validated, the four-category severity class appeared meaningfully related to an important clinical outcome, the patient's desire to continue sildenafil usage after the test period, and to key questions 3 and 4 on the IIEF. The more severe the dysfunction, the less likely is the patient to have a satisfactory response to the drug, irrespective of the traditional classification of organic, psychogenic, or mixed etiology. The potential utility of such a classification system was suggested by the NIH Consensus Development Panel on Impotence.[2] Use of a severity classification, which is simple and easy to apply, appears worthy of further exploration.

A potential source of bias was that 26 (26%) of the 100 study patients failed to complete questionnaires. To resolve this potential bias, we contacted these men by telephone after completion of the study. Eleven men never used the drug, the most common explanation being fear of an adverse event, especially death, which was being reported in the lay press at the time. Two men were lost to follow-up. Of those who had used the drug, 10 reported improved erections and a desire to continue, and 3 reported no benefit and did not plan to continue. Thus, the telephone reports yielded approximately the same proportion of positive and negative responses as in the men who completed questionnaires. The data do not appear to be biased by the men who failed to complete questionnaires.

Before the present report, scant attention was given to the partner's appraisal of therapeutic response in men with ED, despite a clear call for such involvement.[2,7] We modified the IIEF and used it in available partners to assess results of treatment and to substantiate the patient's responses. Both before and after treatment, the partner's responses confirmed the patient's responses ($r = 0.67$ to $0.81, P < 0.01$). This finding must be interpreted cautiously because of the limited number of partners completing the questionnaire (n = 31 to 34) and lack of validation of the modified questionnaire methodology. Nevertheless, the partner confirmations were statistically significant and support a nonquantified, similar finding in the clinical trial.[1] Future study of partner involvement in the evaluation and treatment process would appear warranted.

Sildenafil responses in the 14 men who had ED after radical prostatectomy were disappointing. Only 2 of these men responded favorably to the drug, and in them ED was minimal before sildenafil administration (class I). Should this finding be confirmed in larger studies, the information would be important in future counseling of such men. The relation between surgical technique and response to sildenafil is the subject of ongoing investigation.

CONCLUSIONS

Sildenafil is an effective treatment of ED in a clinical practice setting. Previous data obtained from clinical trials are confirmed. The present findings, based largely on IIEF questionnaire responses, were substantiated by the responses of partners, who independently completed a modified version of the same questionnaire. Classifying the dysfunction according to severity appears to be a simple way to predict treatment response. Men who report some erectile function (severity class I or II) re-

spond to sildenafil much more efficaciously than men with no erections (severity class IV).

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