Efficacy and Safety of Sildenafil in Men With Serotonergic Antidepressant–Associated Erectile Dysfunction: Results From a Randomized, Double-Blind, Placebo-Controlled Trial

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Objective: To evaluate the efficacy of short-term treatment with sildenafil citrate in men with serotonin reuptake inhibitor (SRI)–associated erectile dysfunction (ED).

Method: Men (aged ≥ 18 years) with major depressive disorder (MDD; DSM-IV criteria) in remission and taking SRIs who experienced SRI-associated ED were enrolled in this multicenter, 6-week, randomized, flexible-dose, double-blind, placebo-controlled trial. The primary study measures were questions 3 (Q3: frequency of penetration) and 4 (Q4: frequency of maintained erections after penetration) of the International Index of Erectile Function (IIEF) questionnaire. Secondary study measures were all other questions and domains of the IIEF, the Erectile Dysfunction Index of Treatment Satisfaction (EDITS), a global efficacy questionnaire (GEQ), and a patient-maintained event log of sexual activity.

Results: Patients receiving sildenafil (N = 71) versus placebo (N = 71) reported significantly higher mean ± SE scores on Q3 (3.9 ± 0.2 vs. 3.1 ± 0.2, $p = .003$) and Q4 (3.7 ± 0.2 vs. 2.8 ± 0.2, $p < .001$) of the IIEF and significantly higher scores on all domains of the IIEF. Patients receiving sildenafil also reported significantly improved scores on all questions of the EDITS questionnaire ($p < .02$) and the GEQ ($p < .0001$) and an increased number of successful sexual intercourse attempts per week ($p < .0001$) compared with patients receiving placebo. All patients remained in MDD remission (score ≤ 10 on the Hamilton Rating Scale for Depression). Adverse events in patients taking sildenafil (vs. placebo) were headache (9% vs. 9%), dyspepsia (9% vs. 1%), anxiety (6% vs. 4%), and abnormal vision (3% vs. 0%).

Conclusions: Short-term (6-week) administration of sildenafil was well tolerated and significantly improved erectile function and overall sexual satisfaction in men with ED associated with SRI therapy for MDD. Sildenafil may be successfully used to treat SRI-associated ED without interruption of antidepressant therapy.

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The estimated lifetime prevalence of major depressive disorder (MDD) is 16%, and the 12-month prevalence is 7%, thereby affecting 13 to 14 million U.S. adults each year.[1] Men who suffer from depression have nearly a 2-fold increased likelihood of having erectile dysfunction (ED) compared with men without depression.[2] When ED is a symptom of depression, one would expect that, as depression improves with antidepressant treatment, so too will sexual functioning. However, emergence or exacerbation of ED as a side effect of antidepressant therapy has been reported with almost all antidepressant classes, including monoamine oxidase inhibitors, tricyclic antidepressants, and selective serotonin reuptake inhibitors (SRIs).[3] The emergence or worsening of preexisting ED among patients treated with antidepressants is typically accompanied by psychological and behavioral changes both in those who suffer from it and in their partners.[3] Distinguishing between ED as a symptom of MDD or as a side effect of antidepressant therapy poses a challenge to physicians. Generally, if a patient reports the emergence of ED within 8 to 12 weeks of starting treatment with an antidepressant, it is highly probable that ED is a side effect of the medication. A recent, cross-sectional, observational study conducted in 1101 primary care clinics in the United States, involving 4534 women

and 1763 men receiving antidepressant monotherapy, showed that the prevalence of sexual dysfunction ranged from 7% to 30% in a prospectively defined subpopulation unlikely to have predisposing factors for sexual dysfunction.[4] The odds of having sexual dysfunction were 4 to 6 times greater with SRIs, such as venlafaxine and fluoxetine, than with non-SRIs, such as bupropion.[4]

Of the commonly used antidepressants, SRIs and serotonin-norepinephrine reuptake inhibitors are prescribed to more than 50% of patients.[5] However, studies report tolerance of SRI-induced sexual dysfunction ranging from 25% to 60%,[6,7] which may contribute to the high rate of noncompliance and treatment discontinuation.[4] Approximately 50% of patients discontinue antidepressant therapy after 3 months,[8] and less than 30% complete the recommended 6- to 9-month course of treatment. Premature discontinuation of antidepressant treatment is associated with an increased risk of relapse and recurrence.[9] Managing this side effect is clearly an important aspect in the treatment of depression. In a prospective, parallel-group, randomized, double-blind, placebo-controlled, 6-week, multicenter trial of men with MDD in remission and SRI-associated sexual dysfunction, we previously showed that erectile function, arousal, ejaculation, orgasm, and overall satisfaction domain measures improved significantly in the sildenafil-treated group compared with the group receiving placebo treatment.[10] The upper age limit in the previous study was 55 years, and a relatively small group (N = 45) was randomized to sildenafil. There was also no measure of treatment satisfaction, a key determinant of treatment adherence and continuation. Because sexual function is a component of overall health and quality of life throughout a man's life, in the present study we sought to further these findings of our previous study by examining the efficacy of and satisfaction with treatment with sildenafil in a larger sample of men, with no upper age limit, who were on stable-dose SRI therapy, had SRI-associated ED, and had MDD currently in remission.

METHOD

Study Design

This was a multicenter, 6-week, double-blind, placebo-controlled, parallel-group, flexible-dose (25–100 mg, p.r.n.) study, carried out in centers in the United States, Germany, the United Kingdom, and Canada. The study was approved by the appropriate Institutional Review Boards. All patients signed written informed consent forms prior to study participation. Patients were randomly assigned to receive sildenafil (50 mg) or placebo using a computer algorithm of random permuted blocks and unstratified 1:1 randomization. At a follow-up visit (2 weeks after randomization and dispensation of study medication), patients could adjust their dose to 25 or 100 mg based on efficacy and tolerability.

Inclusion Criteria

Men ≥ 18 years of age with clinically diagnosed MDD (DSM-IV) in remission and in a stable, monogamous relationship were included if they had not had ED before antidepressant therapy, but developed ED following SRI treatment for depression. Erectile dysfunction was determined by a score of ≤ 21 on the Sexual Health Inventory for Men (SHIM).[11] The SHIM is a validated 5-item questionnaire that is commonly used in clinical practice for the diagnosis of ED and to measure the effect of treatment on ED severity. Patients must have been taking a SRI for ≥ 8 weeks at the time of screening and at a stable dose for ≥ 4 weeks. Continued SRI therapy (at the same dose) was required for the course of the study. SRI therapy was considered any treatment with fluoxetine, fluvoxamine, sertraline, paroxetine, venlafaxine, citalopram, or escitalopram.

Exclusion Criteria

Men were excluded if they were symptomatic for depression (Hamilton Rating Scale for Depression [HAM-D][12] score of > 10) despite treatment or were symptomatic for depression and anxiety (Beck Anxiety Index [BAI][13] score > 10) despite treatment. Patients requiring treatment with antipsychotics, mood stabilizers, other nonserotonergic antidepressant agents, or lithium were also excluded (benzodiazepine use was allowed). Men were excluded if they were taking nitrates (a contraindication in the sildenafil label) or any commercially available treatment for ED. Men were also excluded if they had uncontrolled hypertension (blood pressure > 170/110 mm Hg) or hypotension (blood pressure < 90/50 mm Hg) or significant cardiovascular disease within the past 6 months.

Efficacy Measures

The primary study measures were Q3 and Q4 of the International Index of Erectile Function (IIEF).[14] The IIEF is the most commonly used validated instrument in clinical trials of ED treatment. It is brief and reliable, has been used cross-culturally, and is sensitive enough to detect changes in erectile function with ED treatment. Scores were obtained at baseline and after 6 weeks of treatment. Secondary study measures were all domains of the IIEF (scores obtained at baseline and after 6 weeks of treatment); the Erectile Dysfunction Index of Treatment Satisfaction (EDITS),[15] which is a psychometrically valid and commonly used instrument to measure patient satisfaction with ED treatment (scores obtained after 6 weeks of treatment); a global efficacy questionnaire (GEQ), which is commonly used to assess general treatment satisfaction (scores obtained after 6 weeks of treatment); and the percentage of successful sexual intercourse attempts, which was derived from a weekly patient-maintained event log of sexual activity.

Table 1. Baseline Characteristics of Patients Randomly Assigned to Treatment With Sildenafil or Placebo

Variable	Placebo (N = 71)	Sildenafil (N = 71)
Age, mean (range), y	51 (27–74)	51 (28–72)
Weight, mean (range), kg	92 (60–138)	92 (57–157)
Height, mean (range), cm	178 (156–193)	175 (157–191)
Race, N (%)		
White	65 (92)	61 (86)
Black	2 (3)	4 (6)
Asian	0 (0)	2 (3)
Other	4 (6)	4 (6)
Type of antidepressant therapy, N (%)[a]		
Selective SRI	133 (94)	
Serotonin-norepinephrine reuptake inhibitor	10 (7)	
Other antidepressant drug	10 (7)	
Duration of SRI-induced ED, mean (range), y	2.2 (0.2–11.6)	2.7 (0.1–14.2)

[a]Total N = 142. Patients may have been taking more than 1 type of antidepressant.
Abbreviations: ED = erectile dysfunction, SRI = serotonin reuptake inhibitor.

Depression and Anxiety Measures

Depression and anxiety were determined at baseline, for the duration of the study, and at the end of treatment using the HAM-D and BAI, respectively.

Safety

All observed or spontaneously reported adverse events were recorded throughout the duration of the study.

Statistical Analysis

All patients who took at least 1 dose of study medication were included in the safety analysis. Of these, patients who also completed at least 1 efficacy analysis were included in the modified intent-to-treat analysis. Treatment efficacy was determined by 2-sided analysis of covariance performed at the 5% level of significance for ordinal data, and logistic regression was used for binary data.

RESULTS

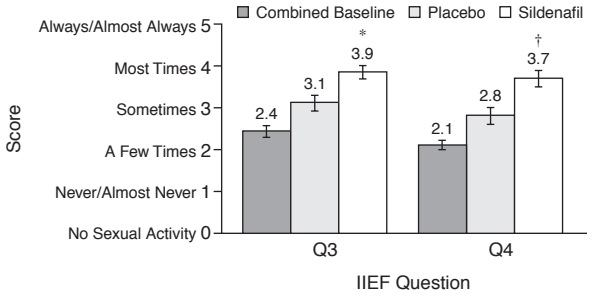
Demographics

In total, 142 men with SRI-associated ED were randomly assigned to sildenafil (N = 71) or placebo (N = 71). Patients in each group were well matched for age, height, weight, race, and duration of SRI-induced ED (Table 1). The types of antidepressant medications did not differ between groups: 94% (N = 133) were taking selective SRIs, 7% (N = 10) were taking serotonin-norepinephrine reuptake inhibitors, and 7% (N = 10) were taking other antidepressant drugs (some patients received more than 1 type of antidepressant).

International Index of Erectile Function

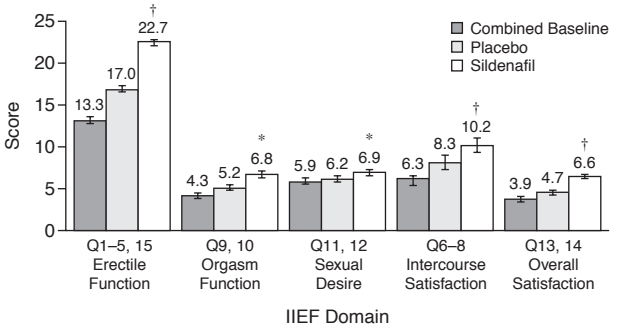
Sildenafil (vs. placebo) treatment was associated with significantly improved scores on Q3 and Q4 of the IIEF (Figure 1). Scores on the IIEF were pooled at baseline because they were not different for patients randomly assigned to receive placebo or sildenafil. However, at the end of treatment, patients who received sildenafil reported scores that were 63% and 76% higher (better function) than baseline scores for Q3 and Q4, respectively, and were significantly higher than placebo scores at end of treatment. Compared to placebo, sildenafil treatment was also associated with significantly improved scores on all domains of the IIEF (Figure 2).

Figure 1. Sildenafil Improved Patient Scores on Question 3 and Question 4 of the International Index of Erectile Function (IIEF)[a]



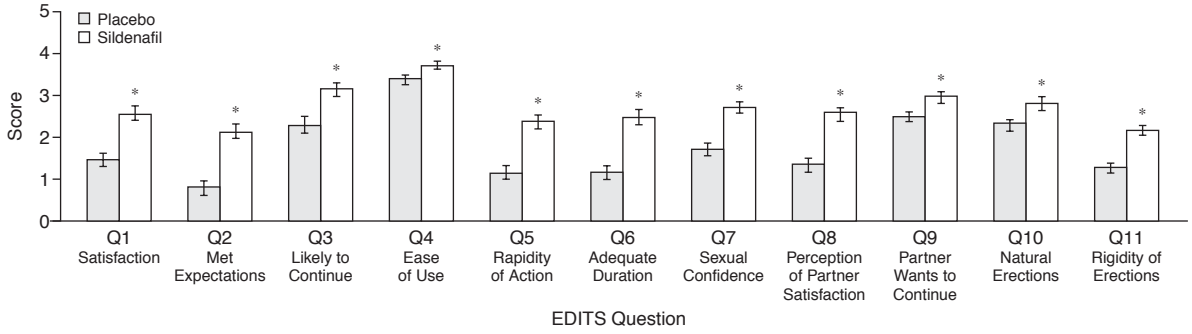
[a]Erectile function was measured using the IIEF at baseline and after 6 weeks of double-blind treatment. Question 3 (Q3) asked, "When you attempted sexual intercourse, how often were you able to penetrate (enter) your partner?" Question 4 (Q4) asked, "During sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner?" Baseline scores were not different between treatment groups and were pooled. Compared with placebo, sildenafil improved the ability to achieve an erection (Q3) and the ability to maintain an erection following penetration (Q4) at the end of the double-blind treatment phase. Higher scores indicate better treatment satisfaction. Scores are shown as mean ± SE.
*p = .003 vs. placebo.
†p < .001 vs. placebo.

Figure 2. Sildenafil Improved Patient Scores on All Domains of the International Index of Erectile Function (IIEF)[a]



[a]Scores (shown as mean ± SE) on the IIEF were recorded at baseline and at the end of the 6-week double-blind treatment with placebo or sildenafil. Baseline scores were pooled for both treatment groups. Higher scores indicate better treatment efficacy.
*p < .05 vs. placebo.
†p < .001 vs. placebo.

Figure 3. Sildenafil Improved Patient Scores on the Erectile Dysfunction Inventory of Treatment Satisfaction (EDITS) Questionnaire[a]



[a]Treatment satisfaction was recorded following 6 weeks of double-blind treatment with placebo or sildenafil. Sildenafil treatment was associated with improved scores on all questions of the EDITS questionnaire. Higher scores indicate better treatment satisfaction. Scores are shown as mean ± SE.
*$p < .02$ vs. placebo.

Table 2. Scores on GEQ Questions and the Event Log of Sexual Function for Patients Receiving Placebo or Sildenafil for 6 Weeks

Measure	Placebo	Sildenafil
GEQ[a]		
Q1: "Compared to having no treatment at all for your erection problem, has the medication you have been taking over the past 4 weeks improved your erections?"	28.8	70.6*
Q2: "Compared to having no treatment at all for your erection problem, has the medication you have been taking over the past 4 weeks improved your ability to have sexual intercourse?"	27.7	72.1*
Q3: "When you took a dose of study drug and had sexual stimulation, how often did you get an erection that allowed you to engage in satisfactory sexual intercourse?"	1.3 ± 0.2	2.5 ± 0.2*
Event log[b]		
No. of sexual intercourse attempts/wk	1.9 ± 0.2	2.6 ± 0.2†
No. of successful attempts/wk	0.6 ± 0.2	1.9 ± 0.2*
Percentage of successful attempts/wk (95% CI)	31 (22 to 43)	71 (60 to 80)*

[a]For the GEQ, values for Q1 and Q2 are percentages of patients who responded "yes." Q3 was scored from 1 to 5, with a higher number indicating a better outcome: 5 = almost always or always, 4 = most times (much more than half the time), 3 = sometimes (about half the time), 2 = a few times (much less than half the time), and 1 = almost never or never. Data are mean ± SE.
[b]On the event log, patients recorded the weekly number of attempts at sexual intercourse and number of successful intercourse attempts. Patients were asked to enter event log data each time they engaged in sexual activity, whether or not they took the study medication, and each time they took the study medication, whether or not they engaged in sexual activity. Data are mean ± SE or mean (95% CI) for the 6 weeks that patients were randomly assigned to study medication.
*$p < .0001$ vs. placebo.
†$p < .01$ vs. placebo.
Abbreviation: GEQ = global efficacy questionnaire.

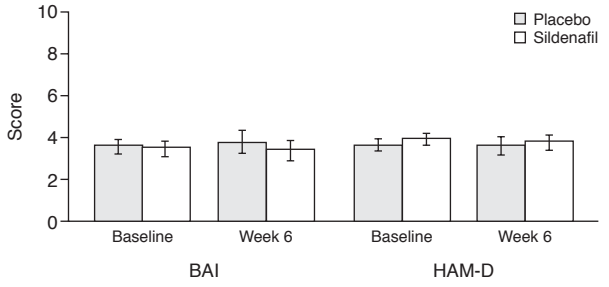
Other Efficacy Measures

Compared to placebo, sildenafil treatment was associated with improved scores on all questions of the EDITS questionnaire (Figure 3). Patients randomly assigned to receive sildenafil reported significantly higher treatment satisfaction (Q1 of the EDITS) and higher satisfaction with attributes of sildenafil such as rapidity (Q5) and duration (Q6) of action, sexual confidence (Q7), and naturalness (Q10) and hardness (Q11) of erections. In addition, compared with placebo, sildenafil treatment was associated with a significantly greater percentage of patients who responded "yes" to Q1 (medication improved erections) and Q2 (medication improved ability for intercourse) of the GEQ, and sildenafil was associated with a nearly 2-fold increase in the frequency of erections that were satisfactory for sexual intercourse (Q3) (Table 2). The score of 2.5 on Q3 of the GEQ for patients who received sildenafil indicated that they had erections hard enough for satisfactory sexual intercourse up to half of the time, compared with the score of 1.3 for patients who received placebo, which indicated that they almost never or never achieved erections hard enough for satisfactory sexual intercourse. Consistent with Q3 of the GEQ, sildenafil was associated with 2-fold (71% for sildenafil vs. 31% for placebo) more successful sexual intercourse attempts per week recorded in the event log of sexual activity (Table 2).

Depression and Anxiety Monitoring

Patients remained in MDD remission and free of significant anxiety. Scores on the BAI and HAM-D question-

Figure 4. Patients Remained in Major Depressive Disorder Remission and Free From Anxiety for the Duration of the Study[a]



[a]Scores (shown as mean ± SE) on the Hamilton Rating Scale for Depression (HAM-D) and the Beck Anxiety Index (BAI) were < 10 at the end of treatment (6 weeks) and were not different from baseline values, indicating no change in depression or anxiety during the 6-week double-blind study.

naires were < 10 at the end of treatment and were not different from baseline scores (Figure 4).

Safety

The mean number of doses taken per month was 13.6 for subjects who received sildenafil and 11.0 for subjects who received placebo. At the end of treatment, 65% of sildenafil patients (46 of 71) chose the 100-mg dose, 34% (24 of 71) remained on the 50-mg dose, and only 1% (1 of 71) chose to take the 25-mg dose. There were no observed or reported serious adverse events. Four patients randomly assigned to sildenafil and 9 patients randomly assigned to placebo discontinued treatment due to protocol violations, but no treatment discontinuations were related to study drug. Adverse events (sildenafil vs. placebo) were headache (9% [N = 6] vs. 9% [N = 6]), dyspepsia (9% [N = 6] vs. 1% [N = 1]), anxiety (6% [N = 4] vs. 4% [N = 3]), and abnormal vision (3% [N = 2] vs. 0% [N = 0]). Abnormal vision in sildenafil clinical trials is generally defined as mild and transient blurry or color tinged vision[16] and is most likely due to the weak inhibitory effects of sildenafil on phosphodiesterase 6 (PDE6), which is uniquely expressed in the retina. Nonarteritic anterior ischemic optic neuropathy, a condition that can result in the sudden onset of partial vision loss, has been observed in a small number of postmarketing spontaneous case reports of patients taking sildenafil. However, no instance has occurred in any controlled clinical trials of sildenafil, including this study.

DISCUSSION

These results confirm previous reports that sildenafil is an effective treatment of SRI-induced ED in male patients[10,17] and are consistent with the therapeutic benefit of sildenafil in the treatment of ED of unknown etiology or as a result of untreated minor depression.[18] In this study, patients were taking SRI antidepressants for at least 8 weeks at the time of enrollment, were on a stable dose of therapy for at least 4 weeks, and were maintained on their stable dose for the duration of the 6-week study. Some patients had been taking antidepressant therapy for as little as 12 weeks, and some for as long as 14 years (Table 1). On average, the duration of SRI-associated ED in our study was greater than 2 years, suggesting the chronicity of this problem. Moreover, sexual side effects of antidepressant therapy tend to subside over time only in the minority of patients, ranging from 5.8% to 9.8% of patients,[6,19] and the emergence of or worsening of preexisting sexual dysfunction often results in premature treatment discontinuation or noncompliance. Satisfaction with treatment is a key factor in adherence and continuation. Our study showed that patients randomly assigned to receive sildenafil were more satisfied with treatment than those who were randomly assigned to receive placebo, and all patients remained on their normal antidepressant medication. Because premature treatment discontinuation or noncompliance can be more costly for depression than for other conditions such as hypertension, hyperlipidemia, or allergy,[20,21] it is not surprising that a recent economic analysis of a hypothetical cohort of 1000 patients taking SRIs for depression demonstrated that adding an effective treatment for ED to current SRI therapy had the lowest cost estimate compared with treatment discontinuation, treatment substitution, or treatment augmentation.[22]

A limitation of this study is that only MDD patients treated with SRIs were included because a cause and effect relationship for sexual dysfunction in patients treated with other antidepressants is less well established. In the power analysis for sample size, it was calculated that 72 patients per treatment group would provide 95% power to detect a difference between treatments at a 5% level of significance. We enrolled and randomized 71 patients per treatment group, which did not quite meet the power analysis requirement. However, the highly significant results with sildenafil ($p < .0001$ in some cases) suggest that 1 patient would not substantially affect the results of this study. Another limitation may be that the patient population was predominantly white. However, studies of patients with ED in Europe, Asia, Africa, and North, South, and Central America show a high degree of efficacy, suggesting that the efficacy of sildenafil is similar across many racial and cultural backgrounds.[23–30]

A 4-year review of sildenafil showed that it has been prescribed for the treatment of ED of wide-ranging etiologies (e.g., vasculogenic, neurogenic, metabolic, endocrine, immune, medical, surgical, idiopathic)[31] and has been found to be more successful than placebo in the treatment of ED in patients with comorbidities such as hypertension,[32] diabetes,[33] and ischemic heart disease[34]

and in men after radical prostatectomy.[35,36] In this study, we showed that 6 weeks of treatment with sildenafil for SRI-induced ED improved erectile function and was well tolerated. Moreover, sildenafil did not interfere with the efficacy of concurrent MDD medication; patients remained in remission. The efficacy of sildenafil after only a brief 6-week course of as-needed treatment suggests that it may quickly treat ED soon after it develops. Moreover, the use of sildenafil appears to be well tolerated and effective across different severities of ED,[37] and patients who have taken it for up to 4 years report high satisfaction with sildenafil treatment.[38] Together, these studies suggest that sildenafil may be effective for early treatment and, potentially, long-term management of ED that develops as a result of SRI therapy for MDD and may help to avoid the potentially harmful effects of antidepressant treatment noncompliance or discontinuation.

Drug names: bupropion (Wellbutrin and others), citalopram (Celexa and others), escitalopram (Lexapro), fluoxetine (Prozac and others), lithium (Lithobid, Eskalith, and others), paroxetine (Paxil, Pexeva, and others), sertraline (Zoloft), sildenafil (Viagra), venlafaxine (Effexor).

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