High-Dose Sildenafil Citrate for Selective Serotonin Reuptake Inhibitor–Associated Ejaculatory Delay: Open Clinical Trial

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Background: Selective serotonin reuptake inhibitor (SSRI)–induced ejaculatory delay is a common problem that has no treatment with established efficacy. Sildenafil citrate is effective for erectile dysfunction and appears to be safe at doses up to 200 mg.

Method: We enrolled men who were in remission from depression according to DSM-IV criteria and who reported that they had developed new-onset ejaculatory delay in the setting of SSRI treatment. Enrolled patients were instructed to use 25 mg of sildenafil 1 hour prior to sexual activity on at least 2 occasions. If this was not effective for the ejaculatory delay, they were instructed to increase the dose progressively up to a maximum of 200 mg. We compared baseline sexual functioning to 2 phases of open treatment: low-dose phase (sildenafil 25–100 mg) and high-dose phase (sildenafil 150–200 mg). The primary outcome measure was a modified, self-report Clinical Global Impressions (CGI) scale that was specific for erectile (CGI-EF) and ejaculatory (CGI-EJF) aspects of sexual function.

Results: Twenty-one men (mean age = 56 years) with major depressive disorder (MDD) in remission and SSRI-associated ejaculatory delay enrolled in the study and received sildenafil. At baseline, 14 of 21(67%) had comorbid erectile dysfunction. At the low-dose phase follow-up assessment, 12 of 14 achieved full erectile dysfunction remission, and 4 of 21 achieved ejaculatory delay remission. Sixteen patients with persistent ejaculatory delay were eligible for the high-dose phase: 5 withdrew from the study, 4 increased to a maximum dose of 150 mg, and 6 increased to a maximum dose of 200 mg. The 1 patient who had clinically significant erectile dysfunction and ejaculatory delay reported improvement of both conditions after the high-dose phase. Of the 10 patients who had ejaculatory delay without significant erectile dysfunction and who chose to take high-dose sildenafil, 9 reported a significant clinical improvement in ejaculatory delay (CGI-EJF improvement score of 1 or 2) and 7 achieved full remission (CGI-EJF severity score of 1 or 2 and CGI-EJF improvement score of 1 or 2).

Conclusion: In this open clinical trial with men who had SSRI-induced ejaculatory delay, high-dose sildenafil appeared to be effective in reducing ejaculatory latency.

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Anorgasmia or ejaculatory delay in males is a sexual disorder for which there are currently few treatment options available.[1] Behavioral therapies have not been shown to be effective in treating this condition, and there are no pharmacologic treatments with documented efficacy. Although ejaculatory delay is generally rare, it is a common side effect of selective serotonin reuptake inhibitor (SSRI) medication.[2,3]

SSRI-induced ejaculatory delay is frequently an intractable clinical problem.[4] This side effect can have a large impact on patients' satisfaction with their antidepressant treatment regimen, can promote medication noncompliance and subsequent depressive relapse, and is associated with reduced quality of life and relationship satisfaction.[2] Although it is difficult to accurately determine the prevalence of SSRI-induced ejaculatory delay because of the variability in SSRI dosing across studies and because sexual function is not systematically assessed in most clinical trials, the most consistent estimates are that at least one third of patients taking SSRIs develop some sexual dysfunction and at least one fourth of men develop ejaculatory delay.[2–6]

Oral sildenafil citrate is an established, effective therapy for patients with erectile dysfunction.[1] Sildenafil is a competitive inhibitor of cyclic guanosine monophosphate (cGMP)–specific phosphodiesterase type 5 (PDE5), the predominant isozyme causing the breakdown of cGMP in the human corpus cavernosum. After sexual stimulation, neurogenically mediated release of nitric oxide induces the formation of cGMP by guanylate cyclase

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within the corpus cavernosum smooth muscle. Sildenafil amplifies the effect of sexual stimulation by retarding the degradation of cGMP by PDE5.[7] As a treatment for erectile dysfunction of mixed etiology, sildenafil has been shown to be safe and effective in men with erectile dysfunction caused by diabetes, spinal cord injury, treatments for prostate cancer, and minor depression.[1,7] Moreover, safety studies have demonstrated that although side effects, such as headache, flushing, visual disturbances, and dyspepsia, are dose-dependent, doses up to 800 mg are generally well-tolerated and without serious adverse effects (R.L. Siegel, M.D., written communication, Nov. 2002).

Although multiple "antidotes" to SSRI-related sexual dysfunction have been proposed, few have been studied in controlled trials, and none has been systematically studied for SSRI-induced ejaculatory delay.[3] In a recent double-blind, placebo-controlled study in 90 middle-aged men, the addition of sildenafil to SSRI treatment was effective for sexual dysfunction.[8,9] However, all of the enrolled men had multiple sexual problems at baseline (mean = 3.5 problems), and 80% had erectile problems. Thus, given the established efficacy of sildenafil for erectile dysfunction, specific improvement in ejaculatory delay could not be distinguished from improved erectile function in this sample.

In assessing men with SSRI-associated sexual dysfunction treated in our depression clinic, we found that most reported that sildenafil treatment led to substantially improved erectile function but persistent ejaculatory delay. However, several patients reported that when they increased the dose of sildenafil to more than 100 mg, they noticed a dramatic improvement in ejaculatory delay. Based on this anecdotal observation and on the compelling clinical need to develop an effective strategy for countering SSRI-induced ejaculatory delay, we performed an open clinical trial with high-dose sildenafil.

METHOD

Study Design

We recruited men, primarily via newspaper advertisements that offered free treatment in a research study, who were 22 years of age or older and currently taking an SSRI. At screening, we obtained demographic information and a medical and psychiatric history. A baseline assessment included a modified Structured Clinical Interview for DSM-IV (SCID)[10] that was limited to assessment of mood and anxiety disorders, a 24-item Hamilton Rating Scale for Depression (HAM-D),[11] and a physical examination. Inclusion criteria were: (1) current use of an SSRI (or venlafaxine) for major depressive disorder (MDD), (2) full remission from MDD with a HAM-D score of less than 8, and (3) SSRI-treatment–emergent ejaculatory delay. We excluded patients who: (1) met diagnostic criteria for any Axis I psychiatric disorder other than sexual dysfunction and MDD in remission; (2) had an acute, severe, or unstable medical condition; or (3) used nitrates in any form. This study was approved by the Institutional Review Board of the New York State Psychiatric Institute and received an investigational new drug (IND) letter of approval from the U.S. Food and Drug Administration. Written informed consent was obtained from all patients before protocol-specified procedures were carried out. Participants did not receive compensation.

Low-dose phase. Patients were instructed to use 25 mg sildenafil citrate 1 hour prior to sexual activity on at least 2 occasions; if they experienced persistent ejaculatory delay at 25 mg, they were to increase to 50 mg, and if they experienced persistent ejaculatory delay at 50 mg, they were to increase to 100 mg. Patients were given a follow-up appointment 4 weeks later. At the follow-up visit, if they continued to have ejaculatory delay they were offered the opportunity to continue treatment in a high-dose treatment phase.

High-dose phase. Patients were instructed to use 150 mg sildenafil citrate 1 hour prior to sexual activity on at least 2 occasions, and if they experienced persistent ejaculatory delay, to increase to 200 mg. Patients were given a follow-up appointment 4 weeks later.

Assessment of Sexual Function

At the time of this study, there was no standard criterion to define response that consistently distinguished ejaculatory delay from other aspects of sexual function and that could therefore be used to detect clinically significant changes in ejaculatory delay over time. Therefore, we developed conservative, a priori response criteria based on the Clinical Global Impressions (CGI)[12] scale as our primary outcome measure. We based this modified CGI scale on both self-reported status and clinician-rated status. One scale focused exclusively on erectile function (CGI-EF), and 1 focused exclusively on ejaculatory function (CGI-EJF). Each CGI scale comprised a severity score and a global improvement score.

For erectile function, the CGI-EF severity score was based on the following question: "Overall, how would you rate your erectile function only over the past 2 weeks?" Patients could answer on a scale from 1 to 7, with 1 reflecting no dysfunction, 2 reflecting borderline dysfunction, and higher numbers reflecting progressively more erectile dysfunction. It was emphasized to patients that an answer of 1 or 2 signified that they had been able to achieve and maintain an erection virtually every time sexual activity was attempted. The CGI-EF improvement score was based on the following question: "Rate your total change in erectile function over the past 2 weeks." A score of 1 ("very much improved") was defined as at least 85% improvement and 2 ("much improved") as at least 60% improvement; higher numbers (3–7) reflected less improvement, no change, and worsening.

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For ejaculatory delay, the CGI-EJF severity score was based on the following question: "Overall, how would you rate your ejaculatory function only over the past 2 weeks?" Patients could answer on a scale from 1 to 7, with 1 reflecting no delay, 2 reflecting borderline delay, and higher numbers reflecting progressively more ejaculatory delay, e.g., 4 ("moderately delayed") was defined by anorgasmia—complete inability to ejaculate—about 50% of the time, 5 ("markedly delayed") was defined by anorgasmia more than 50% of the time, 6 ("severely delayed") was defined by anorgasmia more than 90% of the time, and 7 was defined by complete anorgasmia. It was emphasized to patients that an answer of 1 or 2 signified that they ejaculated when they wanted to, and had no significant ejaculatory delay virtually every time sexual activity was attempted. The CGI-EJF improvement score was based on the following question: "Rate your total change in ejaculatory function over the past 2 weeks." A score of 1 ("very much improved") was defined as at least 85% improvement and 2 ("much improved") as at least 60% improvement; higher numbers (3–7) reflected less improvement, no change, and worsening.

The study psychiatrist (S.N.S.) assessed depressive and sexual symptoms at each visit and confirmed that the CGI-EF and CGI-EJF were consistent with reported sexual function, emphasizing the separate assessment of erectile and ejaculatory function. Full remission of ejaculatory delay was defined a priori by a CGI-EJF severity score of 1 or 2 and a CGI-EJF improvement score of 1 or 2.

The International Index of Erectile Function (IIEF) was completed at every visit. We used only the erectile function (EF) domain as an additional, self-reported measure of erectile dysfunction. The EF domain score ranges from 0 to 30; a score of 21 or below reliably indicates clinically significant (i.e., mild to severe) erectile dysfunction.[13]

All patients were given a complete physical examination at screening and at the end of the study (or at the time of discontinuation). During the study, all adverse effects observed by the investigator or reported by the study participants were assessed for severity and relationship to study medication.

Statistical Methods

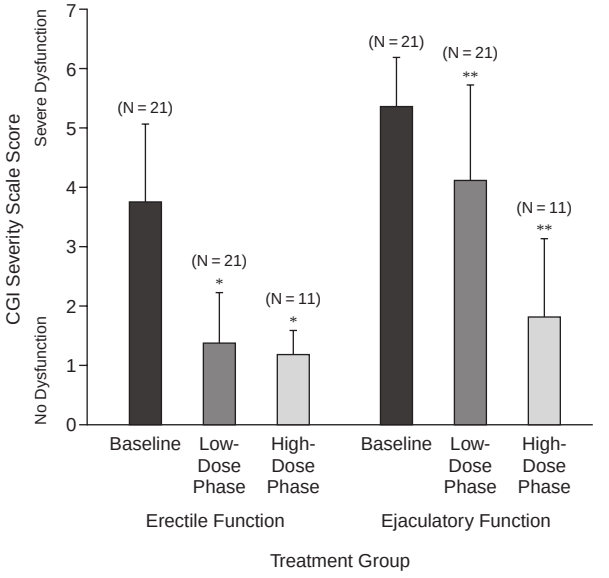
Comparison of continuous data (i.e., CGI severity scores) were analyzed by t tests. All statistical tests were 2-tailed, with an alpha of ≤ .05.

RESULTS

Baseline

Twenty one men (age range, 33–77 years, mean ± SD age = 55.9 ± 14.0 years) with SSRI-associated ejaculatory delay enrolled in the study and received sildenafil. All had MDD in remission. Except for 1 patient who had a depressive relapse after the low-dose phase and was withdrawn from the study, there were no significant changes in measures of mood (i.e., according to HAM-D and Beck Depression Inventory scores, data not shown). At baseline, all 21 men had ejaculatory delay, defined by a CGI-EJF severity score of 4 or higher; the group mean ± SD CGI-EJF severity score was 5.4 ± 0.8. Two thirds (14/21) had clinically significant erectile dysfunction, defined by a CGI-EF severity score of 4 or higher and an IIEF-EF domain score of 21 or below. Mean CGI-EF and CGI-EJF severity scores in the 3 phases of treatment are shown in Figure 1.

Figure 1. Change in Clinical Global Impressions (CGI) Erectile Function and Ejaculatory Function Severity Scale Scores in Men Receiving Low-Dose Sildenafil (25–100 mg) and High-Dose Sildenafil (150–200 mg)



*p < .0001 compared to baseline.
**p < .05 compared to alternative dose treatment.

Change in Erectile Function

Erectile dysfunction remission was defined by 3 criteria: (1) a CGI-EF severity score of 1 or 2; (2) a CGI-EF improvement score of 1 or 2; and (3) a final IIEF-EF domain score greater than 21. Overall, all 14 men with clinically significant erectile dysfunction at baseline achieved remission. Most (12/14) achieved full remission in the low-dose phase (25 mg, N = 3; 50 mg, N = 3; 100 mg, N = 6). Mean ± SD CGI-EF severity scores decreased from 3.76 ± 1.3 at baseline to 1.38 ± 0.84 after the low-dose phase (p = .004) and to 1.18 ± 0.40 after the high-dose phase (p < .001 compared to baseline, and no significant difference compared to the low-dose phase).

Change in Ejaculatory Delay

Study withdrawals. After the low-dose phase, 5 of 21 patients exited the study for clinical reasons: 1 patient had

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a depressive relapse and 4 had fully remitted ejaculatory delay (CGI-EJF severity score of 1 or 2 and CGI-EJF improvement score of 1 or 2). Notably, 3 of 4 responders according to the CGI-EJF had significant erectile dysfunction at baseline, and all achieved full remission after the low-dose phase.

Of the 16 men eligible for the high-dose follow-up, i.e., those with persistent ejaculatory delay and persistent MDD remission, 5 chose not to increase the dose of sildenafil above 100 mg and withdrew consent. All 5 men who withdrew from the study cited safety concerns as their primary motivation. Although all 5 of these patients continued to have significant ejaculatory delay, 2 of 5 who had significant erectile dysfunction at baseline both reported full remission after the low-dose treatment (though persistent ejaculatory delay).

Patients with comorbid erectile dysfunction. One patient who entered the high-dose phase had persistent, significant erectile dysfunction (CGI-EF score = 4 and IIEF-EF domain score = 12). After taking sildenafil 200 mg, this patient had a full remission of erectile dysfunction and a partial remission of ejaculatory delay (final CGI-EJF severity score = 3, CGI-EJF improvement score = 2). Data from this 1 patient with significant comorbid erectile dysfunction are not included in the totals below. However, data from 2 patients who had mild erectile dysfunction and entered the high-dose phase are included in the totals below. Notably, 1 had a full remission of ejaculatory delay (CGI-EJF score = 1, from a baseline score of 5), the second had a partial remission (CGI-EJF score of 3, from a baseline score of 5); in both, erectile dysfunction remitted fully with higher-dose sildenafil.

Patients with primarily ejaculatory delay. Ten men with persistent ejaculatory delay and without significant erectile dysfunction (IIEF-EF domain score ≥ 22) entered the high-dose phase: 4 increased to a maximum sildenafil dose of 150 mg, and 6 increased to a maximum sildenafil dose of 200 mg maximum. Overall, 9 reported significant clinical improvement in ejaculatory delay (CGI-EJF improvement score of 1 or 2) and 7 met criteria for full remission of ejaculatory delay (CGI-EJF severity score of 1 or 2 and CGI-EJF improvement score of 1 or 2). Mean ± SD CGI-EJF severity scores decreased from 5.45 ± 0.93 at baseline to 4.73 ± 1.10 after the low-dose phase ($p < .004$) and to 2.00 ± 1.61) after the high-dose phase ($p < .001$ compared to baseline and compared to low-dose phase).

Overall, 1 patient complained of blue-tinged vision at 200 mg and 1 had a mild headache at 200 mg. There were no other significant adverse events.

DISCUSSION

In this open clinical trial in which men with SSRI-associated ejaculatory delay received successively higher doses of sildenafil, we found that higher-dose treatment was associated with improved ejaculatory function in some men. However, we would note that because there was not a placebo control, these data must be interpreted cautiously. Furthermore, because a substantial number of men were eligible and chose not to receive high-dose treatment, and because changes in erectile function could confound apparent response, ejaculatory delay "response rates" should not be inferred from these data.

The presumed mechanism of SSRI-induced ejaculatory delay is via serotonin-2 ($5\text{-}HT_2$) receptor activation, which is inhibitory to ejaculation, through ascending serotonergic projections to the medial preoptic area and/or descending serotonergic pathways to the lumbosacral motor nuclei.[14] Such activation apparently leads to an increase in genital sensory threshold and the experience of genital "anesthesia." Indeed, multiple case reports and controlled trials now support the effectiveness of SSRIs for the treatment of premature ejaculation: in double-blind, placebo-controlled trials using patient and partner assessments, paroxetine, 40 mg,[15] sertraline, 50 to 200 mg,[16] and fluoxetine, 20 to 40 mg,[17] have been shown to produce significant ejaculatory delay in men with premature ejaculation, i.e., 4 to 10 minutes increased latency to ejaculation. Recent data suggest that some SSRIs may affect sexual function via the reduced production of nitric oxide and through noradrenergic actions.[18] Sildenafil and other PDE-5s might have a prosexual effect through their impact on the nitric oxide system, though the mechanism of the "threshold" effect for reversal of ejaculatory delay suggested by this clinical trial is not apparent.

Strategies for treating SSRI-induced ejaculatory delay include: (1) decreasing the SSRI dose; (2) waiting for tolerance to develop; (3) switching to an antidepressant that does not have sexual side effects; and/or (4) adding an "antidote."[1,3] In anecdotal case reports and some double-blind, placebo-controlled studies,[19,20] multiple antidotes have appeared effective for SSRI-associated sexual dysfunction. Notably, no systematic trial has focused specifically on ejaculatory delay, and no antidote has achieved widespread clinical acceptance. In summary, there is a compelling clinical need to determine the most effective strategy for countering SSRI-induced ejaculatory delay in men, and our preliminary data suggest that high-dose sildenafil is a candidate strategy.

Drug names: fluoxetine (Prozac and others), paroxetine (Paxil), sertraline (Zoloft), sildenafil (Viagra), venlafaxine (Effexor).

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