Sildenafil Citrate for the Management of Antidepressant-Associated Erectile Dysfunction

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Sexual side effects of serotonin reuptake inhibitors, such as antidepressant-associated erectile dysfunction, are common and negatively impact treatment compliance. Current management approaches have important limitations, and most lack clear and meaningful efficacy in double-blind, placebo-controlled trials. A MEDLINE search (English language, 1966–2003) was performed using the terms *antidepressive agents*, *erectile dysfunction*, and *sildenafil*. Emphasis was placed on studies that used specific sexual function measurements and were placebo controlled. Sildenafil citrate, a selective and competitive inhibitor of phosphodiesterase type 5, enhances the cyclic guanosine monophosphate–mediated relaxation of cavernosal smooth muscles in response to sexual stimulation, permitting vascular engorgement and penile erection. The efficacy and tolerability of sildenafil in the treatment of antidepressant-associated erectile dysfunction have been confirmed in double-blind, placebo-controlled trials.

(J Clin Psychiatry 2003;64[suppl 10]:20–25)

Antidepressant medications have been in use for nearly 50 years, and sexual side effects have been reported since the inception of their use. Sexual dysfunction occurs frequently with tricyclic antidepressants and monoamine oxidase inhibitors but is overshadowed by more serious and potentially life-threatening side effects (e.g., ileus, hypotension, cardiac effects). Serotonin reuptake inhibitors (SRIs) rapidly replaced tricyclic antidepressants and monoamine oxidase inhibitors as first-line therapy for depression because they offered easier dose titration, fewer side effects, improved safety, and fewer interactions with other medications.

Unfortunately, as SRIs were more widely used, initial enthusiasm was tempered by the recognition that sexual side effects were even more prevalent than with earlier classes of antidepressants and contributed to high rates of premature discontinuation. Antidepressant-associated sexual dysfunction is a well-described side effect in patients taking SRIs, with the occurrence varying among different agents,[1,2] and it has a significant negative impact on antidepressant treatment compliance. For example, although depressive symptoms in approximately 90% of patients with major depressive disorder (MDD) respond to the first or second antidepressant prescribed, half of all patients discontinue their antidepressant therapy within the first 3 months of treatment, and less than 30% complete the recommended 6- to 9-month course of treatment following remission of acute depressive symptoms.[3] Indeed, patients experiencing intolerable adverse effects are nearly as likely to stop taking their antidepressant (55%) as to ask to switch to another antidepressant (57%).[4] Patients who terminate antidepressant treatment prematurely are at increased risk for recurrence, relapse, and the attendant morbidity/mortality of untreated MDD.[3] Therefore, effective treatment for sexual side effects may improve treatment compliance with antidepressant therapy.

Antidepressant-associated sexual dysfunction is dose-related, reversible, and sometimes transient. Common complaints in men include diminished physiologic arousal (i.e., antidepressant-associated erectile dysfunction), a decline in desire (libido), and difficulty achieving orgasm.[2]

Current management approaches include avoidance of the problem by selecting an antidepressant that has few or no associated sexual side effects, switching to such an antidepressant, use of adjunctive antidote pharmacotherapy with an antagonist or agonist (to counteract pathologic neurophysiology) or with an augmenting antidepressant that has little or no associated sexual dysfunction, and adaptation.[5] However, there are important limitations inherent to these approaches.

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Support was provided by Pfizer Inc, New York, N.Y.

Dr. Nurnberg has served as a consultant to Pfizer, Eli Lilly, SmithKline, Bristol-Myers, and Glaxo; has received grant/research support from Pfizer, Eli Lilly, SmithKline, Bristol-Myers, Abbott, Lipha, Johnson & Johnson, Parke-Davis, and Wyeth; and has served on the speakers bureau for Pfizer, Eli Lilly, SmithKline, Bristol-Myers, Abbott, Glaxo, and Wyeth. Dr. Hensley has received grant/research support from Forest, Pfizer, and Hoffman-LaRoche and has received honoraria from and has served on the speakers or advisory boards for Forest, Pfizer, and Wyeth.

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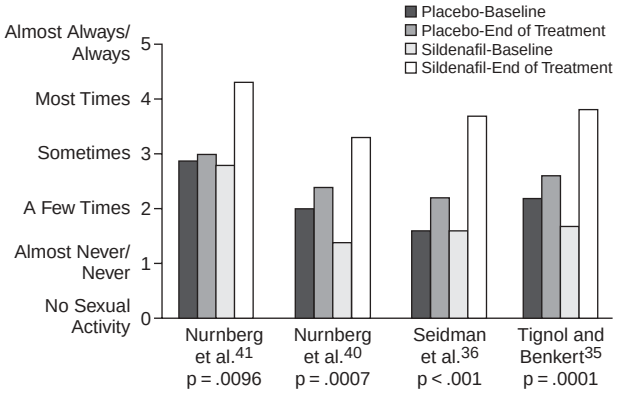
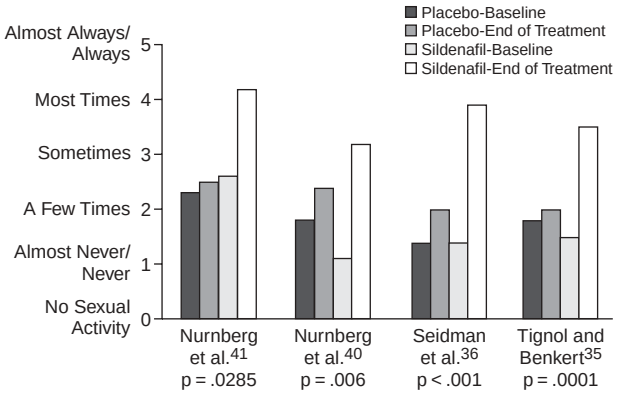
Figure 1. Interstudy Comparison of Mean Responses to Question 3 of the International Index of Erectile Dysfunction (How often are you able to achieve an erection?) After Sildenafil Treatment[a]



[a]Data from Nurnberg et al.[8]

Figure 2. Interstudy Comparison of Mean Responses to Question 4 of the International Index of Erectile Dysfunction (How often are you able to maintain an erection?) After Sildenafil Treatment[a]



[a]Data from Nurnberg et al.[8]

Avoiding, switching, or augmenting effective antidepressant therapy could put depression control at risk; SRIs are not interchangeable, and changing therapy substantially increases the duration of therapy and number of clinic visits and, therefore, possibly cost of treatment.[6] Similarly, adjunctive antagonist or agonist pharmacotherapy to counteract altered neurophysiology might have unwanted side effects, including effects on mood. Waiting an indeterminate period for adaptation to antidepressant-associated erectile dysfunction to occur may put compliance, and consequently depression control, at risk. Finally, for most of these approaches, clear and meaningful efficacy has yet to be demonstrated in double-blind, placebo-controlled trials, and the absence of compelling data is particularly true for the treatment of antidepressant-associated erectile dysfunction.

An optimal therapy would treat antidepressant-associated erectile dysfunction without interfering with the effective control of MDD with SRI antidepressants. It would be administered on an as-needed basis and have a relatively short duration of action to limit exposure and avoid masking adaptation or tolerance to antidepressant-associated erectile dysfunction. Its use would be supported by the results of placebo-controlled, double-blind studies. Sildenafil citrate is widely effective for treating erectile dysfunction of various causes and in numerous clinical populations,[7] and it has been used successfully for treatment of antidepressant-associated erectile dysfunction (Figures 1 and 2).[8]

NEUROPHYSIOLOGY OF ANTIDEPRESSANT-ASSOCIATED SEXUAL DYSFUNCTION

Sexual function is a complex integrated behavior that involves neurohumoral and neurotransmitter systems at both central and peripheral levels of the nervous system.[9] The effects of SRIs on serotonin (5-HT) receptor function are often assumed to induce sexual dysfunction, although the precise mechanisms remain unclear.[9,10] Serotonin is thought to exert inhibitory influences on sexual function, but activation of some 5-HT receptor subtypes, such as 5-HT_{1A}, can facilitate sexual function.[11] In addition, other neurotransmitters (e.g., dopamine, norepinephrine, acetylcholine, nonadrenergic-noncholinergic [NANC]) and peripheral agents (e.g., neuropeptides, hormones, γ-aminobutyric acid [GABA], opioids, prolactin) play essential roles in sexual function.[9]

Prolonged exposure to SRIs can differentially induce changes to 5-HT receptor subtypes that regulate neuroendocrine function in the hypothalamic-pituitary-adrenal, -gonadal, and -thyroid axes.[12] Corticotropin-releasing factor, gonadotrophin-releasing hormone, and thyroid-releasing hormone produced in the hypothalamus stimulate adrenocorticotropic hormone, luteinizing hormone, follicle-stimulating hormone, and thyroid-stimulating hormone release from the pituitary.

Serotonergic receptor changes in the hypothalamus, such as up- or down-regulation that can occur as a consequence of repeated exposure to SRIs, can lead to differential changes in the hypothalamic-pituitary axes that regulate the peripheral release of cortisol, progesterone, estrogen, testosterone, and thyroxine (T_4); growth hormone, prolactin, oxytocin, endogenous opioids, and other peptides are also influenced to varying degrees by 5-HT.[13,14] In turn, monoamine (dopamine, norepinephrine), indolamine (5-HT), cholinergic (acetylcholine), and NANC neurotransmitters are modulated, either directly or indirectly, by alterations in these complex feedback loops. The prevailing hypothesis considers 5-HT to be the most important neurotransmitter mediating the complex

sequence of events that constitute biological (e.g., erection, lubrication) and behavioral (e.g., libido, arousal, orgasm) sexual function.

Two problems limit previous hypotheses on antidepressant-associated sexual dysfunction. The first is reliance on post hoc explanations of sexual dysfunction derived from observed side effects of medication. The second is a lack of awareness of NANC signal transduction, so labeled because it persists in the presence of selective blockade of excitatory adrenergic, cholinergic, and neuropeptide neurotransmission or modulation.

The NANC neurotransmitter of importance in erectile function is nitric oxide (NO). The discovery of the physiologic role of NO in erectile function was initiated by the understanding that acetylcholine is not the primary neurotransmitter in erection but that the endothelium produces a vasoactive substance to relax smooth muscle called endothelium-derived relaxing factor (EDRF).[15] Endothelium-derived relaxing factor was recognized to be NO,[16,17] which initiates a signaling cascade that involves protein phosphorylation and enzyme activation to form cyclic guanosine monophosphate (cGMP).[18] Nitric oxide is produced by nitric oxide synthase (NOS). Neuronal NOS was localized to neurons that innervate the corpora cavernosa and blood vessels of the penis,[19] and electrical stimulation of the cavernosal nerves provokes erection, which is blocked by NOS inhibitors.[20] Thus, NO was established as the neurotransmitter mediating penile erection via stimulation of cGMP formation.[21]

SILDENAFIL FOR THE TREATMENT OF ERECTILE DYSFUNCTION IN MEN WITH DEPRESSION

Phosphodiesterase type 5 (PDE5) is the predominant enzyme responsible for metabolizing cGMP in the corpora cavernosa of the penis.[22] Sildenafil is a selective and competitive inhibitor of PDE5.[23] By inhibiting PDE5 catabolism of cGMP in the corpora cavernosa, sildenafil enhances the cGMP-mediated relaxation of cavernosal smooth muscles, ensuring vasodilation and increased blood flow.[24] This enhancement enables a response to sexual stimulation by acting at the end organ to permit vascular relaxation and engorgement of the lacunar spaces leading to penile erection.[25] PDE5 inhibition by sildenafil also allows for a suitable timeframe for most couples' needs, with onset of action by 30 minutes for the majority of men who respond to it and a duration of action of up to 4 hours.[26]

Sildenafil, approved for use in 1998, has shown efficacy and tolerability in the oral treatment of erectile dysfunction in numerous clinical studies, with documented activity in patients with diabetes,[27,28] hypertension,[29,30] cardiovascular disease,[31] spinal cord injury,[32,33] and multiple sclerosis.[34] In patients with depression, sildenafil is efficacious for erectile dysfunction in those whose depression is untreated and in those being treated with antidepressant therapy. Sildenafil is an effective treatment for erectile dysfunction, whether the depression (disease-related) or antidepressant (iatrogenic) causes erectile dysfunction or the erectile dysfunction causes the depression.

METHOD

A computerized literature search of MEDLINE (English language, 1966–2003) was performed using the search terms *antidepressive agents*, *erectile dysfunction*, and *sildenafil*. To better focus the review, we kept in mind that specific sexual function measurements increase the reporting of antidepressant-associated erectile dysfunction, that baseline data control for the underlying level of erectile function, and that placebo quantifies any placebo effect on underlying sexual function and confirms efficacy. Therefore, emphasis was placed on studies with the following methodological features: specific erectile function measurement before and after treatment and placebo control.

RESULTS

Erectile Dysfunction in Men With Depression

The efficacy of sildenafil for the treatment of erectile dysfunction in men with comorbid depression was first indicated by a retrospective analysis of data from 247 men with a current or past history of depression, which were culled from 11 double-blind, placebo-controlled clinical trials.[7] Sildenafil 25 to 100 mg was taken approximately 1 hour before sexual activity, and efficacy was assessed by scores from question 3 (ability to achieve erection), question 4 (ability to maintain an erection), and the erectile function domain of the International Index of Erectile Function (IIEF). The mean improvement in baseline erectile function scores was significantly higher in those treated with sildenafil than in those treated with placebo ($p < .001$).[7]

More recently, sildenafil efficacy for erectile dysfunction in men with comorbid mild-to-moderate depression was demonstrated by the results of 2 randomized, placebo-controlled trials: the first, in men whose depression was in remission,[35] and the second, in men whose mild depression remained untreated.[36]

Among men in remission from depression who were randomly assigned to treatment with sildenafil (N = 83) or placebo (N = 85), including 84 who had been treated with SRIs, tricyclics, or other antidepressants,[35] the improvement from baseline in IIEF erectile function scores was significantly greater for those receiving sildenafil compared with those receiving placebo ($p < .0001$). Additionally, more men receiving sildenafil reported improved erections (83%) compared with men receiving placebo (34%; $p < .0001$).

Men (N = 152) with untreated mild-to-moderate depressive illness and a mean ± SD erectile dysfunction duration of 5.7 ± 5.6 years were included in a 12-week double-blind trial. A DSM-IV diagnosis of depressive disorder, not otherwise specified, was required for eligibility, but men with MDD were excluded for ethical reasons, because no antidepressant treatment of established efficacy would be provided.[36]

Compared with placebo treatment, sildenafil treatment significantly improved scores on the erectile function domain of the IIEF. Response to treatment was defined as a score of at least 21 out of 30 on the erectile function domain of the IIEF and a positive response to 2 global efficacy questions: (1) Did treatment improve your erections? (2) Did treatment improve your ability to have sexual intercourse? By this rigorous definition, response occurred in 73% (48/66) of sildenafil recipients and 14% (10/70) of placebo recipients.

Interestingly, regardless of whether they were treated with sildenafil or placebo, the mean score on the Hamilton Rating Scale for Depression (HAM-D) improved to a greater extent in treatment responders (10.6 points) compared with nonresponders (2.3 points). Thus, the findings from these studies highlight the importance of a thorough assessment of each patient for erectile dysfunction and comorbid depression to distinguish whether the erectile dysfunction led to depression or is secondary to depression.

Erectile Dysfunction in Men Taking Serotonin Reuptake Inhibitors

The efficacy of sildenafil in the treatment of antidepressant-associated erectile dysfunction was first noted in case reports[37,38] and a small open-label study.[39] Sildenafil efficacy has since been confirmed in a retrospective subanalysis of data culled from several double-blind, placebo-controlled trials[40] and in 2 prospective double-blind, placebo-controlled trials,[41] all of which are detailed below.

Retrospective subanalysis. Ninety-eight men receiving antidepressant treatment with SRIs were identified from among 3409 men evaluated for response in 10 randomized, double-blind, placebo-controlled trials of sildenafil for the treatment of erectile dysfunction.[40] Of these 98 men, 65 received sildenafil (mean ± SD age = 53.8 ± 11.2 years; mean ± SD erectile dysfunction duration = 5.7 ± 5.5 years) and 33 received placebo (mean ± SD age = 51.2 ± 12.0 years; mean ± SD erectile dysfunction duration = 4.9 ± 5.4 years).

Efficacy assessment at baseline and end of treatment (12–26 weeks) indicated that, compared with placebo recipients, sildenafil recipients had significantly greater improvement in mean scores for questions 3 and 4 of the erectile function domain of the IIEF (analysis of covariance, $p < .01$). Furthermore, there was no significant difference in the improvement of erectile function (IIEF questions 3 and 4) between the subgroup taking SRIs and being treated with sildenafil and the subgroup of approximately 2000 men not taking SRIs and being treated with sildenafil. These results indicate that sildenafil is an effective treatment for erectile dysfunction, whether or not concomitant antidepressant treatment with SRIs is being administered.

Double-blind, placebo-controlled trials. The strongest evidence supporting the efficacy of sildenafil in the treatment of antidepressant-associated erectile dysfunction is provided by the results of 2 prospective, randomized, double-blind, placebo-controlled trials in men with MDD in remission and SRI-associated erectile dysfunction. In both trials, sildenafil was initiated at a 50-mg dose, which could be increased to 100 mg if needed.

In the larger trial, 90 men were enrolled on the basis of fulfillment of the following eligibility criteria: 18 to 55 years of age; therapy with a selective or nonselective SRI antidepressant for a minimum of 12 weeks, 6 weeks of which the dosage was stable; antidepressant-associated erectile dysfunction for at least 4 weeks; a history of satisfactory sexual function before the onset of depression or antidepressant treatment; otherwise good health; and regular (minimum once weekly) sexual activity for the study duration.[41]

Sexual function was measured primarily by the Clinical Global Impressions scale adapted for Sexual Function (CGI-SF) and secondarily by the IIEF, the Arizona Sexual Experience scale (ASEX), and the Massachusetts General Hospital-Sexual Functioning Questionnaire (MGH-SFQ). The IIEF is weighted toward erectile function and is not validated in populations with psychiatric disorders, but the ASEX and MGH-SFQ weight sexual dysfunction domains equally and have established use in patients with psychiatric disorders. The study also assessed whether sildenafil treatment affected depression control.

There were no statistically significant differences between patients randomly assigned to sildenafil (N = 45) or to placebo (N = 45) in demographics, duration or type of antidepressant use, and type, severity, or number of sexual problems. Mean ± SD age was 44.9 ± 7.9 years and mean ± SD duration of antidepressant treatment was 27 ± 39.4 months. Improvement from baseline to 6-week endpoint in mean CGI-SF scores was significantly greater for patients treated with sildenafil compared with patients treated with placebo; 55% of sildenafil-assigned men, compared with 4% of placebo-assigned men, achieved "much/very much improved" erectile function, indicating that sildenafil improved antidepressant-associated erectile dysfunction. Furthermore, HAM-D scores at endpoint were not negatively affected; that is, HAM-D scores remained ≤ 10 for all patients, indicating that depression remained in remission, which is the primary goal of antidepressant treatment.

In a small trial, men aged 30 to 64 years (mean ± SD age = 45.7 ± 8.5 years) were randomly assigned to receive

sildenafil (N = 11) or matching placebo (N = 10) for 8 weeks of double-blind treatment.[42] All men were free of organic causes of erectile dysfunction, and all medication, including SRIs, were stabilized for at least 4 weeks before enrollment and for the duration of the trial. At baseline, total ASEX scores and nocturnal penile tumescence and rigidity measured by RigiScan (Timm Medical Technologies, Eden Prairie, Minn.) were comparable between the 2 groups. ASEX scores improved (decreased) from baseline to end of treatment in both groups, with a 2-fold greater decline in the sildenafil group (6.0 points) compared with the placebo group (2.9 points) in total score and a significant improvement in the sildenafil group compared with the placebo group for item 3, which measured erectile function ($p < .006$).

In these 2 double-blind, placebo-controlled trials, sildenafil was well tolerated. In the larger trial, headache (41% sildenafil vs. 10% placebo) and flushing (7% sildenafil vs. 2% placebo) were the most commonly reported adverse events. Similarly, in the second trial, headache (55% vs. 9%) and flushing (55% vs. 0%) were the most commonly reported adverse events among sildenafil versus placebo recipients.

SUMMARY

Well-designed trials of sildenafil have clearly established efficacy for the treatment of antidepressant-associated erectile dysfunction. Studies have also shown that sildenafil does not interfere with SRI control of depression. Moreover, sildenafil is taken on an as-needed basis and has a relatively short duration of action, thereby limiting exposure and avoiding the masking of adaptation or tolerance to antidepressant-associated erectile dysfunction. Further research is warranted to determine whether the efficacy of sildenafil in treating antidepressant-associated erectile dysfunction can be extended to other pharmacologic interventions associated with erectile dysfunction, such as typical neuroleptics, atypical antipsychotics, mood stabilizers, anticonvulsants, benzodiazepines, and other psychotropic medications.

Thorough assessment to identify the etiology of erectile dysfunction and effective treatment are important components of the overall clinical management of patients with depression. Given the evidence in favor of sildenafil and the lack of convincing supportive evidence for other management strategies, sildenafil can be considered a first-line treatment for antidepressant-associated erectile dysfunction.

Drug name: sildenafil citrate (Viagra).

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