

# Letters to the Editor

## Safety of Sildenafil for Antidepressant-Related Sexual Dysfunction

**Sir:** I wish to call your attention to a possible safety issue in the report on the use of sildenafil for antidepressant-related sexual dysfunction.<sup>1</sup> Although the authors screened their patients for medical illness and reported no serious adverse reactions to sildenafil in these antidepressant-treated subjects, the use of this agent in patients taking nefazodone (as in cases 1 and 3) may pose some risk. Nefazodone is a substantial inhibitor of the cytochrome P450 3A4 (CYP3A4) enzyme system,<sup>2</sup> which also metabolizes sildenafil.<sup>3</sup> In theory, this could lead to abnormally high blood sildenafil levels, which, in turn, may be associated with elevated cardiovascular risk and other adverse events.<sup>3</sup> Thus, clinicians who attempt to treat sexual dysfunction with sildenafil should exercise caution when patients are taking concomitant nefazodone or other CYP3A4 inhibitors.

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**Ronald Pies, M.D.**  
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### Dr. Nurnberg and Colleagues Reply

**Sir:** We read with interest the letter from Dr. Pies. The cytochrome P450 enzyme system is certainly an important factor to consider in prescribing all medications. There may be some disagreement, however, in how strongly, and with what clinical significance, nefazodone inhibits the CYP3A4 enzyme.

According to Preskorn, "Ketoconazole related antifungal agents and several macrolide antibiotics (e.g., erythromycin) can substantially inhibit this enzyme [CYP3A3/4]. Fluvoxamine, norfluoxetine and . . . nefazodone also inhibit this enzyme, but are substantially less potent than ketoconazole in this regard."<sup>1</sup>(p155) He then explains that the potency of enzyme inhibition of the SSRIs and nefazodone has been overstated. Of the antidepressants, fluvoxamine is the most potent in vitro CYP3A3/4 enzyme inhibitor and has been shown in vivo to be a 20- to 100-times less potent inhibitor of CYP3A3/4 than antifungals such as ketoconazole when clinically relevant dosing conditions are observed. Nefazodone is one tenth as potent as ketoconazole at inhibiting this enzyme in vitro.<sup>1</sup>

In terms of clinical significance, we agree with Gelenberg that "when drugs are added to or deleted from any treatment regimen, it is safest to assume an interaction and then search for evidence."<sup>2</sup>(p42) He suggests that nefazodone may inhibit the metabolism of drugs degraded by CYP3A4 and that the doses of

such medications may need to be adjusted downward. As always, we need to listen to our patients, watch for drug interactions, and, being cognizant of potential P450 interactions, anticipate them. We did that in our study.<sup>3</sup> Patient 3 reported no adverse effects after taking sildenafil. Patient 1, however, did report a transient headache. Of note, she also reported rapid resolution of sexual dysfunction with just 50 mg of sildenafil. These observations are consistent with the report by Fava et al.<sup>4</sup> in which a starting dose of sildenafil, 50 mg, reversed nefazodone treatment-emergent sexual dysfunction without adverse effect. Perhaps we can use lower doses of sildenafil, such as 25 mg, with patients who are concurrently taking a medication that inhibits CYP3A3/4. Another consideration is that some patients, who under other circumstances might need a higher dose (i.e., 100 mg) for full therapeutic effect, may be able to respond to a lower dose when taking another medication that inhibits CYP3A3/4.

Dr. Pies' point is well taken and suggests further consideration of how to clinically apply cytochrome P450 enzyme information. Sildenafil is a short-acting drug (half-life = 4 hours) that is primarily excreted fecally (80%), has other CYP enzymes involved in its metabolism (2C9), and has an active metabolite of 50% potency and 40% plasma concentration of parent drug; the metabolite accounts for 20% of sildenafil's pharmacologic effects.<sup>5</sup> Consequently, complete inhibition of CYP3A3/4 enzyme production could increase potency by approximately 60% or give a 50-mg dose the more prolonged potency of an 83-mg dose of sildenafil. Because nefazodone only mildly to moderately inhibits CYP3A4, this potential effect can be expected to be attenuated. Although no drug interaction is without potential risk, for CYP enzyme systems, the eventuality of the actual occurrence of such interactions is not certain. Even if interactions do occur, the result can be adverse, but also beneficial or of no significant effect. Therefore, while knowledge about cytochrome P450-mediated potential interactions is extremely important and useful, it also should not be overstated to absolutely mean that drugs with such potential effects cannot be used together.

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### Treatment of Kleptomania With Paroxetine

**Sir:** Kleptomania is characterized by the recurrent failure to resist impulses to steal objects that are not needed for personal use or for their monetary value.<sup>1</sup> Further, patients experience a sense of tension immediately before the theft and a sense of pleasure or relief upon committing the theft.<sup>1</sup> This disorder is listed in DSM-IV under impulse-control disorders not elsewhere classified. In some patients, however, the principal effect of the theft is the relief of tension, suggesting that kleptomania may be a form of obsessive-compulsive disorder (OCD).<sup>2</sup> This concept of the disorder has led to the use of selective serotonin reuptake inhibitor (SSRI) medications for pharmacologic management. Here, I report a case of kleptomania effectively treated with paroxetine.

**Case report.** Mr. A, a 29-year-old white man, presented to the outpatient clinic on referral from the local state psychiatric hospital. He had been admitted to the hospital 1 month earlier following a suicide attempt. While in the hospital, paroxetine, 20 mg each day, was begun for treatment of major depressive disorder. At his first outpatient visit, he continued to endorse symptoms of depression, including "somber" mood, poor sleep and appetite, anhedonia, impaired concentration, feelings of helplessness and guilt, and persistent crying spells. He denied current suicidal ideation. He also denied any symptoms consistent with a past or present history of mania or hypomania. In addition to major depressive disorder, Mr. A revealed a long history (> 10 years) of impulsive stealing. He had never before revealed this problem, although he had been fired from a number of jobs because of stealing. He stated that the intrinsic value of the object was unimportant—"It could be something as worthless as a pen to money I didn't need and wouldn't spend." He described an "adrenaline rush" prior to the theft and experienced a great sense of relief following the theft. He said that he typically stole items "about twice a week." Importantly, he stated that his stealing behavior could occur exclusive of any mood disturbance (i.e., he stole while not depressed).

Because of his continued depression and the obsessive-compulsive-like quality of the kleptomania, paroxetine was increased to 30 mg each day, and follow-up was arranged. He missed his original follow-up appointment and instead returned to the clinic 3 months later. He had been noncompliant with appointments because he had been out of town (he had obtained a job that required frequent travel), but he had been compliant with medication. At this visit, all depressive symptoms were in remission. However, Mr. A was more impressed by the fact that his compulsion to steal had "all but vanished." He said he still had fleeting thoughts of stealing, but that he was easily able to control his behavior. He had not stolen since his previous visit, and the same company had employed him for the past 3 months, a long period for Mr. A.

A search of the literature reveals that Mr. A represents the first reported case of kleptomania successfully treated with paroxetine. There are other reports in the literature indicating beneficial effects of SSRIs in the treatment of adult kleptomania, including treatment with fluvoxamine<sup>3</sup> and fluoxetine.<sup>4,5</sup> At the time of our evaluation, Mr. A's kleptomania was comorbid with major depressive disorder. However, in his past history, kleptomania had been present exclusive of any mood disorder. Likewise, although kleptomania has been observed to be comorbid with bipolar disorder,<sup>6</sup> Mr. A never exhibited symptoms of mania or hypomania. The presence of Mr. A's stealing behavior ex-

clusive of mood symptoms, the good response of his symptoms to SSRI medication, and the overlap of his symptoms with those of OCD suggest that Mr. A's kleptomania might be best conceptualized as a form of OCD. Thus, in cases similar to Mr. A's, a medication trial with an SSRI might be beneficial. It is important to note that although Mr. A had a favorable response to SSRI pharmacotherapy, SSRI medications have been reported to worsen kleptomaniac behavior.<sup>7</sup>

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### Self-Amputation of Left Hand: A Case Report

**Sir:** Dr. Schlozman, in the December 1998 issue of the *Journal*, report 2 cases of upper-extremity self-amputation.<sup>1</sup> Published reports, reviewed in his article,<sup>1</sup> mostly date from the 1970s or 1980s. In recent years, the progress in psychiatric and surgical care may have changed the incidence and outcome of this rare complication of psychosis.

**Case report:** Mr. A, a 34-year-old man, was admitted to the Department of Surgery at the Medical Centre (Ljubljana, Slovenia) after self-amputating his left hand at the radiocarpal joint and making several deep incisions on his right wrist. In the emergency unit, Mr. A was agitated, yelling, and uncooperative. He was sedated with haloperidol and diazepam and went to surgery, where the left hand was replanted. However, the functionality of his left radiocarpal joint could not be preserved, and an arthrodesis was made. Eight days later, Mr. A was transferred to a psychiatric hospital because of continuing agitation despite neuroleptic treatment and lack of compliance with postoperative care. This was his first contact with a psychiatric service. Mr. A, a former student of philosophy who gave up study some 5 years ago, was unemployed. His girlfriend had not noticed any changes in his mood or daily functioning in the weeks preceding his self-amputation. At admission, he was quiet, answering only 1 or 2 questions. He was oriented to time and place, but his affect was flat and inappropriate. The next day, he explained that he has been hearing commanding voices for 2 to 3 weeks and was convinced that he was changing into a devil. The only chance to stop this transformation was to cut off both hands. Therefore, he first incised his right wrist and later

amputated his left hand with a kitchen knife. He did not feel any pain and calmly went out of the house, where he met his girlfriend and told her that "I am finally free."

Mr. A was first treated with parenteral haloperidol and promazine and later with oral fluphenazine. During hospitalization, he complied well with medication and rehabilitation procedures. There were no attempts of repeated self-harm. Hallucinations and delusions vanished after 3 weeks of treatment, and Mr. A was discharged 2 weeks later with a diagnosis of schizophreniform disorder. According to current treatment recommendations,<sup>2,3</sup> we started maintenance depot neuroleptic treatment with 25 mg of fluphenazine decanoate monthly. Up to now, 13 months after discharge, the patient is free of psychotic symptoms and has continued his study. After rehabilitation, the surgical outcome is also favorable. Mr. A can move the fingers of his left hand; however, the sense of touch is still lacking.

Self-amputation is a very rare condition, as in the last 10 years we have encountered only the presented case among more than 30,000 admissions. We agree with Dr. Schlozman on the need for replantation (even in case of the patient's refusal). Since the patient often has to be transferred to a psychiatric service early after surgery because of noncompliance, agitation, or continuing acts of self-harm, close cooperation of surgeons and psychiatrists is vital. In long-term maintenance treatment, depot neuroleptics may have the advantage over oral drugs because of better compliance.

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### Recommended Haloperidol and Risperidone Doses in First-Episode Psychosis

**Sir:** Dr. DeQuardo<sup>1</sup> has produced a comprehensive review and discussion of the issues in early intervention in schizophrenia and other psychoses. In general, I found the review useful in drawing together a range of recent evidence supporting this expanding area of interest in psychiatry.

The one flaw in his article, and one that is critical in a review focused on pharmacologic treatment, is the dose ranges suggested for use in first-episode patients. Although Dr. DeQuardo stresses the importance of setting the stage for long-term management and getting treatment off on the right foot, the dose ranges advised for risperidone and haloperidol are substantially higher than necessary in this population of patients. For example, the 1991 study by McEvoy et al.<sup>2</sup> showing that a mean dose of 2.1 mg of haloperidol was effective in the first-episode patients is not emphasized. With regard to risperidone, it is now widely acknowledged that the initial dose ranges originally advised for this drug were significantly overstated. In our unit, a

dose-finding study of 96 patients treated with risperidone found that 60% of patients achieved a good response at 4 weeks after commencing treatment with 2 mg of risperidone. A modest increase in doses to 3 mg or even 4 mg over the next few weeks was associated with some additional response; however, in the group as a whole, the mean dose for the initial 10-week period of treatment was 2.8 mg of risperidone. One of the major aims is to avoid extrapyramidal symptoms (EPS) in this population, and we have found that a substantial number of patients will start to develop EPS once the dose is elevated beyond the 2 mg of risperidone. Some patients can tolerate up to 4 mg, but not much more than this without developing neurologic side effects. The evidence in relation to olanzapine from our clinical experience is more in accord with the dose range reported in Dr. DeQuardo's article,<sup>1</sup> i.e., 10 to 20 mg/day.

I hope these comments are of interest and will assist in avoiding overdosing neuroleptic-naïve patients.

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#### Dr. DeQuardo Replies

**Sir:** I appreciate the opportunity to reply to Prof. McGorry's letter regarding my article. Prof. McGorry expresses the concern that I may have recommended larger than necessary doses for risperidone and haloperidol in first-episode schizophrenia. He goes on to cite a study by McEvoy et al.<sup>1</sup> demonstrating that haloperidol at 2.1 mg/day is effective in treating first-episode patients, as well as his own work suggesting that risperidone in the dosage range of 2 to 4 mg/day is effective in treating 60% of patients with first-episode psychosis. Prof. McGorry's main point is that low doses of these 2 agents are necessary in order to avoid EPS and thus enhance patient compliance with treatment early in the course of illness.

I must first say that I agree completely with Prof. McGorry's concern about potentially overdosing antipsychotic-naïve patients early in the course of illness, resulting in noncompliance and interfering with development of a relationship with the treatment team. However, the doses of haloperidol (6-10 mg/day) and risperidone (4-8 mg/day) recommended in my article are in keeping with my clinical experience and are in a range that the vast majority of patients will need to receive to obtain maximum benefit after months of slow medication titration. As pointed out by Prof. McGorry, some patients do respond to very low doses of these medications. However, the dosage ranges that I recommend cover the vast majority of first-episode patients treated with these agents.

The reference that Prof. McGorry cites supporting the use of very low doses of haloperidol was not cited in my study. The article by McEvoy et al.<sup>2</sup> that I reference, although involving many of the patients in the study cited by Prof. McGorry, is not the same study by McEvoy et al.<sup>1</sup> that he cited. Indeed, studies such as those cited by Prof. McGorry, although clearly beneficial in beginning to outline efficacy of various antipsychotic

medications in first-episode psychosis, highlight the difficulty in making generalizations from controlled studies to routine clinical practice, where the reality of severe constraints on duration of available treatment mandates rapid and sometimes aggressive intervention. Furthermore, in my article, I cited several published reports (e.g., Lieberman et al. [1993],<sup>3</sup> McCreddie [1996],<sup>4</sup> Kopala et al. [1996]<sup>5</sup>) documenting the safety and efficacy of these agents at the doses I recommended for first-episode schizophrenia.

I am certain that Prof. McGorry and I have many more areas where we agree than where we disagree regarding pharmacologic treatment of first-episode psychosis. Rather than quibble about doses, I would prefer to emphasize several of the messages that I had put forth in my article, and that are highlighted in Prof. McGorry's letter, namely, that early intervention in first-episode psychosis is crucial and involves low doses of antipsychotic medication, both typical and atypical with very slow titration and documentation of clinical benefit as well as toxicity. Clearly, minimizing extrapyramidal symptoms and other side effects related to pharmacologic treatment is vital in enhancing patient compliance and quality of life; these symptoms are important to attend to as a result. First-episode psychosis provides the clinician with an opportunity to initiate definitive treatment and develop a long-term relationship with patients, which together will optimize outcome.

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#### Paroxetine for Primary Insomnia: Possible Placebo Effect?

**Sir:** Primary insomnia is widely prevalent, resulting in considerable distress and impairment. A new drug that is not a controlled substance, is nonhabituating, and that does not leave the patient sedated during the day would be a welcome addition to the pharmacopoeia. I read with interest the article by Nowell et al.,<sup>1</sup> which reported an uncontrolled, open study of the treatment of primary insomnia with the selective serotonin reuptake inhibitor antidepressant paroxetine in 14 patients. However, I find their conclusion that paroxetine is effective in the treatment of insomnia unjustified by the data presented.

There was a significant treatment response according to the subjective evaluation of the patients, but not by any of the objective polysomnography measures including quantity of sleep time, number of awakenings, or the architecture of sleep. In view of the expected correlation of the subjective patient evaluation and objective polysomnography measures,<sup>2</sup> and the power of the

placebo effect in the treatment of insomnia, one has to conclude that the apparent response is primarily a placebo effect.

To this date, there is no convincing evidence that non-sedating antidepressants are effective in the treatment of primary insomnia. However, I agree with the authors that double-blind, placebo-controlled studies are needed. At the least, such studies would shed light on the powerful placebo effect, which remains insufficiently understood and underutilized in medicine.

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#### Once-Daily Venlafaxine XR Compared With Fluoxetine in Outpatients With Depression and Anxiety

**Sir:** We read with interest the study conducted by Silverstone et al.<sup>1</sup> which reaffirms the efficacy of fluoxetine in patients with anxiety and depression.<sup>2-4</sup> However, the authors' statement in the abstract claiming that this study "provides evidence for [venlafaxine XR's] superiority over fluoxetine"<sup>1(p22)</sup> is unfounded and may mislead readers who have not had the opportunity to critically review the article. A thorough review of this study plainly demonstrates that fluoxetine has comparable efficacy to venlafaxine XR and better tolerability.

Both fluoxetine and venlafaxine XR provided significant improvements on the Hamilton Rating Scale for Depression (HAM-D), the Hamilton Rating Scale for Anxiety (HAM-A), and the Clinical Global Impressions-Improvement scale at study endpoint ( $p < .05$  vs. placebo). They were also statistically significantly superior to placebo at study endpoint on the following secondary efficacy variables: HAM-D factor subscores (except sleep disturbance item), the Hospital Anxiety and Depression scale, the Covi Anxiety Scale, HAM-D response rate, and HAM-D remission rate. Although venlafaxine XR was superior to fluoxetine at week 12 on the HAM-A, this difference is likely due to random noise, since there were no significant differences between these 2 drugs on the HAM-A at any other timepoints, including study endpoint. Also, we were surprised by the authors' use of combined HAM-D and HAM-A response rates to demonstrate a difference between high-dose venlafaxine XR and fluoxetine at week 12. This finding is difficult to interpret because these scales are independent measures that have not been previously combined or validated in the published literature, the analysis was conducted post hoc, and the higher response rate noted with venlafaxine XR was clearly accounted for by the HAM-A score at a single timepoint. Furthermore, the inclusion of SSRI nonresponders likely biased this result in favor of venlafaxine XR.

In terms of tolerability, the fact that venlafaxine XR-treated patients experienced greater numbers of specific adverse events compared with both fluoxetine-treated and placebo-treated patients further questions the authors' assertion of superiority. During the study, patients treated with venlafaxine XR experienced significantly more insomnia, nervousness, and anorexia when

compared with those treated with placebo, and significantly more dizziness and sweating compared with both placebo- and fluoxetine-treated patients. In contrast, only insomnia was reported significantly more often in patients treated with fluoxetine than in those treated with placebo. Also, although the overall incidence of nausea was not significantly different between active treatment and placebo, the incidence of nausea at week 1 was notably higher with venlafaxine XR than with either fluoxetine or placebo (statistical analysis not provided).

In summary, the authors' use of isolated timepoints, post hoc analyses, and unvalidated statistical methods seriously undermines their attempt to claim that this study "provides evidence for superiority over fluoxetine" and that "drugs with combined serotonergic and noradrenergic reuptake blockade may be more efficacious than drugs blocking serotonin reuptake alone."<sup>1(p27)</sup> Quite simply, the results from this study suggest only that fluoxetine and venlafaxine XR are equally effective in ambulatory patients with depression and comorbid anxiety, and that fluoxetine is better tolerated.

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#### Drs. Silverstone and Ravindran Reply

**Sir:** Drs. Judge and Wagner question the conclusion from our study that venlafaxine XR "provides evidence of superiority over fluoxetine." Their main reason for questioning this conclusion is their belief that the statistically significant differences at week 12 between the venlafaxine XR-treated patients and the fluoxetine-treated patients on the Hamilton Rating Scale for Anxiety (HAM-A) are due to "random noise." Their major justification for this position appears to be that there were no previous statistically significant differences between the 2 drugs at other timepoints. However, they fail to note that at weeks 8 and 12, the venlafaxine XR group showed statistically significant differences from the placebo group, whereas the fluoxetine group showed no such statistically significant differences from the placebo group at either timepoint. Thus, despite the reservations of Drs. Judge and Wagner, we remain convinced that this is a genuine and interesting finding, suggesting differences in effectiveness between these 2 drugs in this patient population.

Drs. Judge and Wagner also question the use of the combined HAM-A and Hamilton Rating Scale for Depression (HAM-D) scores in this patient population. We agree that this is not a common method of analysis for data from these instruments. However, as clearly described in the article, the purpose of this study was to try and "determine the medication effects in patients with both major depression and anxiety by combining results from the HAM-D and HAM-A scales."<sup>1(p26)</sup> We pointed out that few studies have examined patients with this overlap of disorders and that in our opinion the use of these paired outcome criteria provides a more relevant overall perspective for the global outcome in this patient population. We believe that this approach may well be useful in other studies that examine patients with comorbid depressive and anxiety disorders.

In addition, what Drs. Judge and Wagner do not discuss is the increasing evidence that combined action at serotonergic and noradrenergic receptors appears to increase antidepressant effectiveness more than does selective serotonin reuptake alone. The increased effectiveness of dual action has been shown for tricyclic antidepressants combining dual receptor uptake inhibition,<sup>2</sup> a combination of SSRIs and specific noradrenergic receptor antagonists,<sup>3</sup> and drugs that combine serotonergic and noradrenergic receptor effects, namely venlafaxine,<sup>4</sup> mirtazapine,<sup>5</sup> and milnacipran.<sup>6</sup> Most of these studies have been carried out in patients with major depressive disorder and concomitant severe illnesses.

Therefore, we believe that while SSRIs remain very useful medications, our study is one of a series adding support to the notion that agents with effects on serotonergic and noradrenergic neurotransmitter systems may be more efficacious compared with drugs that act on only the serotonergic system. This may be specifically relevant to a more treatment-refractory group such as patients with major depressive disorder with significant anxiety.

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