# Letters to the Editor

## Relief of SSRI-Induced Sexual Dysfunction With Mirtazapine Treatment

**Sir:** Sexual dysfunction is a known integral component of depressive illnesses, and most antidepressant drugs have been associated with sexual dysfunction, especially those agents with increased serotonergic activity.[1–4] In fact, the use of selective serotonin reuptake inhibitors (SSRIs) has been associated with significant ejaculatory dysfunction and orgasm-related difficulties.[1,4–6] However, the incidence of sexual dysfunction varies with SSRIs. The package inserts report a range from 2% (fluoxetine) up to 20% (sertraline, paroxetine),[5,7] and in the clinical setting, sexual dysfunction has been reported to occur in 7.8% to 75% of depressed patients.[5–8] These differences in reported incidences may be due to a number of factors including duration of study, patients' inhibitions about reporting sexual dysfunction, lack of inquiry on the part of the clinician, or differences in the parameters used to elicit sexual function information (i.e., rating scales).[1,4,5,7] In the study with the highest incidence of sexual dysfunction, patients were routinely questioned about their sexual function.[8]

Various strategies have been used to manage antidepressant-induced sexual dysfunction; these include drug holidays, lowering the dosage, switching agents, and adjunctive therapy.[5–7,9] Spontaneous reductions in sexual side effects have been reported toward the end of a 6- to 8-week treatment period.[1,2] However, in the clinical setting, patients may not wait for spontaneous reductions and often discontinue their antidepressant therapy. Agents such as cyproheptadine, yohimbine, and amantadine have been reported to be helpful as adjunctive therapy.[10–12] Other strategies include switching to an antidepressant that does not carry this risk: bupropion, nefazodone, or mirtazapine.[1,5,13–15]

Mirtazapine, a potent 5-$HT_2$ and 5-$HT_3$ antagonist along with $\alpha_2$-antagonistic properties, has been reported to have little or no incidence of sexual dysfunction.[3,16] Since sexual side effects related to SSRI treatment are believed to be mediated through 5-$HT_2$ stimulation, possible relief of symptoms may result from blocking these receptors with mirtazapine.[16,17] Reports that mirtazapine reverses sexual side effects of ongoing SSRI therapy led to the following case reports.[13–15]

The following case series describes 4 patients who experienced sexual dysfunction while on SSRI therapy and consented to a trial of add-on, open-label mirtazapine therapy. Response to sexual functioning was either spontaneously reported (2 patients) or actively elicited (2 patients).

***Case 1.*** A 47-year-old woman with a past medical history of alcohol dependence and premenstrual syndrome responded to paroxetine, 20 mg/day, for panic attacks and generalized anxiety, yet lack of libido was noted by 8 weeks of therapy. She had previously discontinued treatment with fluoxetine, 40 mg/day, for 1 year because of sexual dysfunction. She reported sexual intercourse at least 2 times per week (baseline libido) prior to SSRI therapy. Mirtazapine, 15 mg at bedtime, was added, and at her next medication check 6 weeks later, she reported restoration of baseline sexual desire. Return of normal libido remains after 5 months of treatment with mirtazapine.

***Case 2.*** A 30-year-old woman with a past medical history for chronic depression (> 3 years) had been treated with numerous antidepressants such as sertraline, venlafaxine, and bupropion with no response. However, this patient did respond to treatment with fluoxetine, 30 mg/day, but complained of loss of libido after 6 weeks of therapy. Mirtazapine, 15 mg at bedtime, was added, and libido returned to baseline within 2 months. This patient has sustained her normal libido for 3 months of mirtazapine treatment.

***Case 3.*** A 36-year-old woman with a past medical history for posttraumatic stress disorder after a car accident responded well with paroxetine and zolpidem therapy. After 3 weeks of treatment with paroxetine, 30 mg/day, anorgasmia and decreased libido became prominent. Both of these symptoms improved within 1 week of initiating treatment with mirtazapine, 15 mg at bedtime. However, she discontinued this agent due to weight gain associated with increased appetite.

***Case 4.*** A 49-year-old woman with depression reported "no sexual desire" after 2 months of paroxetine therapy. Her daily dose of paroxetine was 30 mg/day, and she was also taking clonazepam, 0.5 mg twice a day, for anxiety and insomnia. Mirtazapine, 15 mg/day, was added to her regimen at bedtime, and within a month she reported restoration of normal libido. Since then, her libido has been sustained for 2 months of mirtazapine treatment.

The cases reported herein demonstrate that mirtazapine may be beneficial in patients with SSRI-induced sexual dysfunction. These findings are consistent with the clinical pharmacology of mirtazapine, in that blockade of 5-$HT_2$ receptors may be related to lack of sexual side effects. All 4 patients reported resolution of their sexual side effects, which included anorgasmia and lack of libido, shortly after mirtazapine was added to their regimens. Criticisms of these cases may be that not all patients were questioned about sexual dysfunction and rating scales were not used to determine the level of sexual dysfunction at baseline, after initiation of SSRI therapy, and after initiation of mirtazapine therapy. However, once it was determined that the patients had sexual dysfunction, they were successfully treated with mirtazapine. Another concern could be that mirtazapine may have been added too early to the drug regimen. However, mirtazapine therapy was added after at least 6 to 8 weeks of SSRI therapy, which would have allowed for spontaneous reductions in sexual dysfunction. In most instances reported in the literature, the level of sexual dysfunction decreases by the end of the first 8 weeks of SSRI therapy.[1,2] However, this was not the case with my patients because sexual function had not improved over the first 8 weeks of their SSRI therapy. One patient discontinued mirtazapine therapy because of weight gain.

SSRI therapy is known to carry the risk of sexual dysfunction,[1–4] and clinicians are often faced with the challenge of finding effective treatment strategies without compromising patient response to a particular agent. Controlled investigation is war-

ranted to fully determine the effect of mirtazapine on SSRI-induced sexual side effects.

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## Obsessive-Compulsive Symptoms With Risperidone

**Sir:** The recent letters from Dr. Andrade[1] and Drs. Saxena and Bystritsky[2] regarding the worsening of antidepressant-treated obsessive-compulsive symptoms upon addition of risperidone did not address an additional issue—that there have been reports of risperidone-induced obsessive-compulsive symptoms.[3,4] In addition, I recently had a patient who developed an obsessional image of a person's face that repeatedly appeared in his mind as he went about his activities. He did not know the person whose image he saw, and he became acutely distressed by the recurring appearance of this image. This patient had a diagnosis of schizophrenia with no past history of obsessive-compulsive symptoms and had been on treatment with risperidone, 4 mg/day, for 18 months. He was also receiving sodium valproate, 1000 mg/day; benzhexol, 4 mg/day; and a depot injection of zuclopenthixol, 400 mg every 2 weeks. The recurrent images disappeared after the dosage of risperidone was decreased to 3 mg/day.

It is likely that risperidone's potent serotonin ($5\text{-HT}_2$) antagonism has a role in the occurrence of obsessive-compulsive symptoms. Combinations of a serotonin reuptake inhibitor (SRI) and risperidone therefore would require close monitoring for a possible exacerbation of obsessive-compulsive symptoms.

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## Dr. Andrade Replies

**Sir:** Dr. Mahendran presents a case of obsessive imagery in a schizophrenic patient. She suggests that risperidone was responsible for the phenomena. Militating against her argument is the long duration (18 months) of uneventful use of risperidone. Favoring her argument is the disappearance of symptoms when the dose of risperidone was lowered. In the absence of mention of potentially dysequilibrating and re-equilibrating psychopharmacologic or psychosocial events, it is assumed that none existed. Rechallenge with risperidone was not attempted. Essentially, the etiologic role of risperidone in this case, while possible, remains unconfirmed.

Dr. Mahendran observes that I did not address risperidone-*induced* obsessive-compulsive symptoms in my report; since the issue was peripheral to my subject, I had mentioned risperidone-induced *worsening* of such symptoms, but merely in passing. My report addressed a hazard of the risperidone-fluoxetine combination; Dr. Mahendran describes a hazard of risperidone monotherapy.

Dr. Mahendran suggests that $5\text{-HT}_2$ receptor antagonism with risperidone may underlie its propensity to induce or worsen obsessive-compulsive symptoms. Although most authors would agree, I believe that the mechanisms are far more complex. Consider the following: serotonin reuptake inhibitors (SRIs), in the long term, induce compensatory down-regulation of several presynaptic and postsynaptic serotonergic receptors,[1] whereas risperidone produces a direct, functional blockade of these receptors.[2] In addition, SRI drugs produce downstream dopaminergic inhibition,[3] whereas risperidone directly blocks dopamine receptors.[2] Such serotonergic and dopaminergic mechanisms may be therapeutically relevant in obsessive-compulsive disorder (OCD).[4,5]

These similarities of action suggest that risperidone may potentiate the action of SRI drugs in OCD. So, why would risperidone monotherapy or rapid dose escalation with risperidone

precipitate or exacerbate obsessive-compulsive symptoms? The answer may lie in time-dependent changes: the described receptor actions of SRI drugs are delayed, whereas those of risperidone are immediate. Consequently, it is likely that SRI therapy primes the biological system in some hitherto unknown way, making later serotonergic and dopaminergic receptor changes therapeutic. Gradual dose escalation with risperidone, hypothetically, similarly allows the system to adapt. In contrast, risperidone monotherapy, rapid dose escalation, or high-dose treatment with risperidone overwhelms the receptors and does not allow the development of the putative compensatory therapeutic mechanisms.

This hypothesis explaining SRI-risperidone synergism has a homeopathic flavor. There is little better to offer, however, to explain the otherwise paradoxical observations that risperidone can both benefit as well as precipitate and/or worsen obsessive-compulsive symptoms, depending on the circumstances. In any case, Dr. Mahendran's concluding note is valid: that the SRI-risperidone combination requires close monitoring for possible exacerbation of obsessive-compulsive symptoms, a point which I, too, made in my report.

As a tailpiece: the patient described in my original letter[6] remained moderately to severely impaired 6 months after his initial exacerbation of obsessive-compulsive symptoms associated with risperidone use. After obtaining informed consent, he was rechallenged with risperidone (1 mg/day); his existing dosage of fluoxetine (60 mg/day) was continued unchanged. Amelioration of obsessive-compulsive symptomatology was observed. After 1 month, the dosage of risperidone was raised to 2 mg/day. There was rapid loss of the accrued gains. The dosage of risperidone was therefore lowered and maintained at 1 mg/day; this dosage was associated with acceptable response. These observations fit the argument that has been offered for the mechanism of risperidone-fluoxetine synergism. Further research with in vivo chemical challenges may, however, provide more information about the mechanisms involved.

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## Dr. Saxena Replies

**Sir:** In his letter, Dr. Mahendran correctly observes that the recent letters from Andrade[1] and from Saxena and Bystritsky[2] did not discuss the issue of risperidone-induced obsessive-compulsive symptoms. However, both de novo obsessive-compulsive symptoms and exacerbations of obsessive-compulsive symptoms associated with risperidone and clozapine were reviewed in a previous report by our group[3] on risperidone augmentation of SRI treatment for refractory OCD. In recent years, several more cases have added to our understanding of this phenomenon.

A review of the existing literature on obsessive-compulsive symptoms associated with atypical antipsychotics leads us to several general conclusions. First, obsessive-compulsive symptoms induced by atypical antipsychotics occur much more frequently in patients with schizophrenia and other primary psychotic illnesses than in patients with primary OCD or Tourette's disorder. Of the total of 17 patients with atypical antipsychotic–induced obsessive-compulsive symptoms (10 with clozapine,[4–7] 6 with risperidone,[8–12] and 1 with olanzapine[13]) described in the literature, only 1 patient[12] had primary OCD without a comorbid primary schizophrenia spectrum illness. Patients with schizophrenia may have central serotonergic system abnormalities[14] that predispose them to the development or worsening of obsessive-compulsive symptoms during treatment with atypical antipsychotics, which are all strong antagonists at a variety of 5-HT receptors.[15] There have been reports of obsessive-compulsive symptoms improving or remaining unchanged in patients with Tourette's disorder[16,17] and other OCD spectrum disorders[18] treated with risperidone, but no reports of obsessive-compulsive symptoms worsening in those patients. A second conclusion is that obsessive-compulsive symptoms most often occur with atypical antipsychotic monotherapy and improve with the addition of an SRI.[4,7,9,10,12] Third, obsessive-compulsive symptoms are seen much more commonly during treatment with higher doses of atypical antipsychotics (e.g., above 3 mg/day of risperidone or 10 mg/day of olanzapine) than with lower doses. Hence, starting at low doses and increasing slowly appear to be prudent recommendations for atypical antipsychotic augmentation of SRIs.

The mechanisms and risk factors for atypical antipsychotic–induced obsessive-compulsive symptoms remain unclear. Clearly, more research is needed to help practitioners avoid this troubling, if relatively uncommon, adverse effect. Such research will also improve our basic understanding of the neurobiological mediation of obsessive-compulsive symptoms.

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## Can Long-Term Antidepressant Use Be Depressogenic?

**Sir:** We appreciated the thoughtful review on the loss of antidepressant efficacy by Byrne and Rothschild.[1] We would like to put forward another possible explanation for the observation: long-term antidepressant use may be depressogenic. While this idea seems counterintuitive, there are reasons to seriously consider it. It has become clear that long-term use of antidepressants may destabilize patients with bipolar illness and give rise to dysphoric mixed states or rapid cycling,[2–4] despite the fact that the initial effect of antidepressants in these subjects is therapeutically antidepressant.[4]

It is not uncommon for the chronic effect of a drug to be different from the initial effect. The best psychiatric example is that of the classic antipsychotics. The acute motoric effect of these drugs is bradykinetic (parkinsonism), but the chronic effect is hyperkinetic (tardive dyskinetic choreoathetoid movements).[5] It has been postulated that a neuroleptic-induced increase in the number of synapses or perforated synapses[6,7] may underlie this change. Similarly, neuronal sprouting of serotonergic neurons in the simple nervous system of snails can be modified with long-term alteration of serotonin concentrations,[8,9] raising the possibility that antidepressant agents may cause neuroplastic changes. In other words, it is possible that antidepressant agents modify the hardwiring of neuronal synapses not only to render antidepressants ineffective but also to induce a resident, refractory depressive state. Although this proposal is purely speculative, the possibility needs to be considered.

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## Drs. Rothschild and Byrne Reply

**Sir:** We appreciate the comments of Dr. El-Mallakh and colleagues regarding our article[1] on the loss of antidepressant efficacy during maintenance therapy and their interesting suggestion that long-term antidepressant treatment may itself be depressogenic. In our article, we did offer this as one of several possible explanations for the phenomenon of loss of antidepressant efficacy. A change in the depressive disease due to medication therapy may be secondary to decreased dopaminergic tone owing to direct or indirect antidopaminergic effects of the antidepressant[2] or long-term changes in neurotransmitter systems, analogous to the changes by which antidepressants may destabilize patients with bipolar disorder. In addition, as was discussed in our article, tricyclic antidepressants may shorten the time between recurrences in unipolar depressive illness as well as in bipolar disorder.[3] We also speculated that the long-term use of antidepressants could cause the depletion of one or more effector or precursor substances. For example, serotonin reuptake inhibition, by increasing extrasynaptic serotonin levels, could in theory cause a depletion of tryptophan in the brain by down-regulating the mechanism by which tryptophan is transported across the blood-brain barrier. Another example, as pointed out by Dr. El-Mallakh and colleagues, is that the neuronal sprouting of serotonergic neurons in the central nervous system of snails can be modified with long-term alteration of serotonin concentrations.[4,5]

We agree with Dr. El-Mallakh and colleagues that the hypothesis that antidepressants may be depressogenic is speculative. We have not observed the phenomenon of antidepressant tachyphylaxis ("poop-out") to be a permanent or refractory state. In fact, there are many strategies discussed in our article[1] that are effective for treating a loss of antidepressant efficacy. One of these strategies, raising the dose of the antidepressant, is by far the most popular strategy[6] and has been reported to produce full remission in 67% of patients who experience loss of antidepressant efficacy during fluoxetine treatment.[7] If long-term treatment with antidepressants were depressogenic, one would expect that raising the dose of the antidepressant would make the patient worse, not better. Finally, as we discussed in our article, the clinical presentation of loss of antide-

pressant efficacy often differs from the initial presentation of the depressive syndrome, with depressed mood, apathy, and fatigue returning, but not the vegetative symptoms of depression. Clearly, further studies are needed to ascertain the rate of loss of antidepressant efficacy during maintenance treatment, whether it occurs more often with a particular type of antidepressant, and whether there are particular patients who are more at risk for the occurrence of loss of efficacy.

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## Environmental Factors in Panic Disorder

**Sir:** Recently, mental health professionals in the Anxiety and Depression Clinic at Montefiore Medical Center, New York, noticed that a substantial subgroup of patients with panic disorder described hot weather and humidity as potential triggers of panic attacks. Since these findings raised important questions concerning the role of environmental factors in panic disorder, Montefiore clinicians developed a questionnaire to systematically evaluate the prevalence of hot weather, humidity, and various other conditions as catalysts for panic attacks. The questionnaire asked patients to rate on a scale from 0 to 3 whether panic was triggered or worsened by such conditions (0 = never, 1 = sometimes, 2 = most of the time, and 3 = always). Patients (N = 154) participated by completing the questionnaire and undergoing a semistructured interview to establish a DSM-IV diagnosis of panic disorder.

After review of the data, some patterns became quite evident. Over 53% of patients endorsed that humidity either caused or worsened panic attacks at least some of the time. Moreover, 65% responded that hot weather also had such an effect. While these findings are only preliminary, they clearly reinforce the notion that humidity and hot weather are important environmental factors in panic disorder. Two recent articles[1,2] support such a conclusion, yet no study has ever systematically assessed the prevalence of hot weather and humidity as environmental factors in panic attacks. Furthermore, it is unclear whether such conditions are specific or nonspecific anxiogenic stressors. Regarding the latter, heat stress can induce autonomic arousal, resulting in symptoms such as increased heart rate and sweating,[3] which may precipitate a panic attack in panic disorder patients who tend to be overly sensitive to visceral cues.

In addition to hot weather and humidity, other environmental factors such as organic solvents and gases have been reported to induce panic attacks in patients with multiple chemical sensitivity syndrome, which is a controversial syndrome and may represent a subgroup of panic disorder.[4]

Certainly, our findings may have a number of important clinical implications. First, mental health professionals should be advised as to the potential association that apparently exists between environmental factors and panic attacks. Such an awareness serves to lend credence to patient accounts that incorporate environmental conditions. Second, and more importantly, the findings present a potentially viable treatment strategy in managing panic attacks in environmentally dependent patient subgroups. In many patients who are adversely affected by hot weather and humidity, a cool, climate-controlled area is frequently able to subdue or alleviate attacks. To this end, clinicians could advise patients to properly moderate temperature in their home environment. In extreme cases, relocation to a suitable environment may be advisable. However, regardless of application, the findings suggest a new, optimistic avenue in the continuing fight against panic disorder.

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