Letters to the Editor

Is Risk of Neuroleptic Malignant Syndrome Increased in the Postpartum Period?

Sir: Although there is no definite consensus, many factors (e.g., high-potency neuroleptics, higher dose of neuroleptics, parenteral administration of neuroleptics, rapid dose escalation, concurrent use of lithium and neuroleptics, affective disorder, organic brain syndrome, agitation, fluid and electrolyte imbalances, shifts in cholinergic-dopaminergic balances, genetic factors) have been proposed to increase the risk for occurrence of neuroleptic malignant syndrome (NMS).[1,2] However, due to the rarity of the syndrome, speculation about the etiologic importance of these factors is based on reviews of case reports or retrospective and prospective studies involving small sample sizes. It is likely that many cofactors that increase the vulnerability for the development of NMS are yet to be identified. Even though the occurrence of NMS has been reported in the postpartum period,[3,4] this time period has not been specifically suggested as a risk factor.

To identify the correlates of NMS, we conducted a prospective study spanning 30 months between 1994 and 1996 in a university general hospital that is a referral center for a large geographic area of 2 southern states of India. All the patients seen by one of us in an adult psychiatric unit during this period, which was on duty 3 times a week, were screened for NMS. These patients included those receiving treatment at the psychiatric outpatient department, patients referred from other departments (outpatients and inpatients) and patients who were referred to us by emergency service, and all patients admitted into our unit during the study period. Diagnosis of NMS was made on the basis of operational criteria proposed by Carroff et al.[5] Other physical diseases that could explain the symptoms were carefully ruled out in all patients by appropriate investigations in consultation with the faculty of the neurology and internal medicine departments.

During the study period, NMS was detected in 11 patients (5 women and 6 men). Of these, 9 patients had developed NMS while receiving treatment for their psychiatric illness elsewhere. Three of our sample of patients with NMS had onset in the postpartum period. Their ages ranged from 22 to 26 years. All 3 of them had elevated temperature (100°F–104°F), rigidity, dysphagia, mutism, elevated blood pressure, tachycardia, and profuse sweating. The creatine kinase levels were 33, 626, and 3020 U/L (normal range, 10–80 U/L). One patient had a mixed affective episode, and each of the other 2 had a major depressive episode, severe, with psychotic features. One of the 3 patients had an additional diagnosis of moderate mental retardation, which can increase the risk of development of NMS.[1] Of the 3 patients, 1 developed NMS after 4 days of treatment with chlorpromazine, 20 mg/day; another after 21 days of treatment with amoxapine, 100 mg/day; and the third after 3 days of treatment with trifluoperazine, 20 mg/day, and chlorpromazine, 100 mg/day. All 3 were judged to be dehydrated at the time of initial assessment, and 1 had evidence of hypernatremia and hyperkalemia based on electrolyte estimation. None of these patients had puerperal infection or other medical illnesses to account for their symptoms, and none was taking any other medication known to enhance the risk of NMS.

Even though NMS can occur with low doses and in the therapeutic range of neuroleptics, it generally occurs with higher doses of neuroleptics or rapid dose escalation.[1,2,6] To our knowledge, occurrence of NMS with chlorpromazine 20 mg/day orally has not been reported. Although we have come across 7 cases of NMS occurring in association with treatment with amoxapine,[7–13] most cases of NMS have been reported in association with treatment with neuroleptics.[1,2,14] The fact that 60% of the women in our sample (3/5) developed the syndrome during the postpartum period and the fact that NMS occurred in association with treatment with an extremely small dose of oral chlorpromazine in 1 patient and in association with treatment with an antidepressant in another suggest the possibility of an increased risk of occurrence of NMS in the postpartum period. Affective disorders, agitation, and electrolyte imbalance, which were present in all 3 of our patients, are likely to be common in psychiatric syndromes occurring in the postpartum period. These have been proposed to increase the risk of occurrence of NMS.[1,2,6,14] Alternatively, it is speculated that the rapid hormonal changes (e.g., progesterone, estrogen, cortisol, thyroid) that can trigger puerperal psychiatric disorders[15] can lead to alteration in dopaminergic, cholinergic, GABA, adrenergic, calcium, and serotonin metabolism, thereby increasing the vulnerability for the genesis of NMS.

The sample size of our study was very small, and we have no data on the total number of patients in the general population with postpartum psychiatric disorders who were prescribed neuroleptics and who developed NMS. Similarly we have no data on the total number of patients in the general population who were prescribed neuroleptics and who developed NMS. Also, in the previous 2 reported cases of NMS occurring in the postpartum period,[3,4] patients were on high doses of antipsychotics. Hence, to corroborate our speculation of possible increased risk of NMS in postpartum psychosis, further prospective studies using a larger sample size and appropriate statistical techniques to discount the effect of confounding variables are required.

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FINISH: Remembering the Discontinuation Syndrome

Sir: The recent article by Schatzberg et al.[1] helps physicians increase their awareness of the discontinuation syndrome that may occur when patients stop taking their antidepressants. It is now clear that many physicians are unaware of the existence of antidepressant withdrawal symptoms and that education is needed for both psychiatrists and family practice physicians.[2] In order to improve recognition of the symptom clusters that constitute the discontinuation syndrome, I have introduced the mnemonic FINISH, indicating the symptoms that may occur when patients "finish" their course of antidepressants.

Flu-like symptoms, ***I***nsomnia, ***N***ausea, ***I***mbalance, ***S***ensory disturbances, and ***H***yperarousal (anxiety/agitation) are the 6 core symptoms that sometimes develop after discontinuation of antidepressant therapy. Awareness of this mnemonic should increase recognition of the syndrome and improve the advice given to patients with respect to discontinuation of their medications.

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Risperidone May Worsen Fluoxetine-Treated OCD

Sir: Several recent studies have suggested that risperidone may usefully augment serotonin reuptake inhibitor (SRI) therapy in refractory obsessive-compulsive disorder (OCD). One study[1] found that 14 of 16 refractory OCD patients experienced substantial improvement in obsessive-compulsive symptoms within 3 weeks of the initiation of an SRI-risperidone combination; indeed, certain patients improved dramatically within days. A second study[2] reported that 7 of 14 OCD patients responded with the addition of risperidone after having failed to respond to SRI therapy alone. A retrospective chart review[3] discovered that 8 patients with OCD who had failed an SRI trial responded within a month of supplementation with risperidone.

Several case studies have also reported that OCD patients who had failed isolated SRI trials or who had failed multiple therapeutic interventions (with SRIs and other drugs administered singly or in combination) subsequently responded to risperidone augmentation of an SRI.[4–6] In many instances, the addition of risperidone elicited dramatic improvement. With a few exceptions, the dose of risperidone used in most of these studies and reports was low (4 mg/day or less).

These encouraging results notwithstanding, it must be kept in mind that the SRI-risperidone combination may also elicit negative results. An educative case is described below.

Case report. Mr. A, a 21-year-old unmarried man, was diagnosed with OCD (DSM-IV) of 6 years' duration. There was no comorbid disorder. The chief symptoms included counting, checking, and washing compulsions. Mr. A also had compulsive rituals for various daily activities. Much of his time was spent in illness behavior, to the extent that he was unable to undertake socially desirable activities. After 2 months of treatment with fluoxetine in a dose that was stepped up to 60 mg/day, the intensity of his symptoms decreased by about 75%; he was able to resume his studies and even appear for a university examination. However, no further improvement accrued over the following 6 months, despite the initiation of a behavior therapy program involving relaxation, response prevention, and related elements.

Risperidone was then added to the fluoxetine regimen in a dose that was stepped up to 3 mg/day over 3 days. There was an immediate and catastrophic deterioration, with the severity of obsessive-compulsive symptoms returning to pretreatment levels. There were no symptoms, however, that could have been considered as adverse effects of risperidone. Continuation of the combination over the next 2 weeks caused no further change. Reduction of the dose of risperidone to 1 mg/day, and then to 0.5 mg/day (each dose maintained for a week), also had no benefit. Risperidone was withdrawn, and Mr. A was continued on fluoxetine treatment alone. Over the next 3 months, he gradually began to recover but did not reattain the pre-risperidone status.

Saxena et al.[1] have correctly reviewed the literature that describes risperidone-induced deterioration in OCD; however, they hypothesize that such deterioration occurs only with risperidone monotherapy. This case report suggests that some patients may deteriorate with the SRI-risperidone combination as well. There are at least 2 possible reasons to explain the worsening described in this case. One is that fluoxetine may have inhibited the metabolism of risperidone, leading to the patient's exposure to higher levels of risperidone than the daily dose seemed to warrant. Another is that the dose of risperidone may have been

raised too rapidly; successes[1–6] with the SRI-risperidone combination have in general described the use of low doses that are very gradually raised over the course of several weeks.

When risperidone is used to augment SRI therapy in refractory OCD, it is therefore advisable to start with low doses of risperidone, to raise the dose very gradually, and to watch for possible deterioration.

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Drs. Saxena and Bystritsky Reply

Sir: We read with interest the letter by Dr. Andrade describing a patient with SRI-refractory OCD whose symptoms were exacerbated after adjunctive risperidone was added to ongoing fluoxetine treatment. We urge caution, however, in making any conclusions about the efficacy or tolerability of risperidone augmentation of SRI treatment based on the reactions of a single patient. In addition to our study of risperidone augmentation in 26 SRI-refractory OCD patients,[1] several other reports describe the therapeutic value of adding risperidone to an SRI[2] or clomipramine[3] for refractory OCD as well as related OCD-spectrum disorders, such as trichotillomania and Tourette's syndrome.[4]

Several factors could potentially cause symptom exacerbation when risperidone is added to fluoxetine, including pharmacokinetic and pharmacodynamic interactions, and side effects such as akathisia or anxiety that can exacerbate OCD symptoms. Our group has also seen symptom exacerbations in a small number of OCD patients after combining SRIs and risperidone, but these exacerbations were usually secondary to the development of akathisia with combination treatment. Because fluoxetine inhibits the cytochrome P450 2D6 enzyme system,[5] which metabolizes risperidone to 9-hydroxyrisperidone,[6] combining the 2 drugs may result in high plasma levels of risperidone, increasing the likelihood of side effects. Competition for protein binding sites could produce higher free plasma levels of both risperidone and fluoxetine, also increasing the risk of side effects. Dr. Andrade's letter did not mention whether his patient developed akathisia or other side effects that could contribute to symptom exacerbation when risperidone was added to fluoxetine. Nor did the letter describe any comorbid conditions the patient may have had that could have influenced his response to risperidone augmentation.

Another factor that could account for the symptom exacerbation experienced by Dr. Andrade's patient is the rapid escalation of risperidone dose to 3 mg/day within 3 days. In our study and that of Stein et al.,[4] the average doses of adjunctive risperidone after 4 weeks were 2.75 mg/day and 1.625 mg/day, respectively, usually starting with 0.5 mg/day and titrating upward very slowly. There have been several reports of increased incidence of adverse events associated with rapid titration of risperidone.[7,8] Therefore, we recommend initiating risperidone at very low doses when adding it to an SRI, and caution against rapid increase of risperidone dose.

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Nefazodone and the Treatment of Panic

Sir: In a recent review of antidepressants used in treating panic disorder, Dr. Jefferson[1] thoroughly reviews the historical data pertaining to tricyclics, monoamine oxidase inhibitors, and serotonin selective reuptake inhibitors (SSRIs). He makes brief mention of other antidepressants such as venlafaxine, bupropion, trazodone, as well as inositol, but no mention of nefazodone.

The highlights of a panic disorder symposium from the 8th Annual U.S. Psychiatry Congress are summarized in the *Journal*.[2] Nefazodone is mentioned, but no studies are cited. Our literature search, addressing the use of nefazodone for panic, revealed 1 open-label trial of nefazodone in high comorbidity panic disorder[3] and 1 retrospective analysis of 2 randomized, placebo-controlled trials evaluating the effectiveness of nefazodone in relieving depression-associated anxiety symptoms.[4] The patients in both studies were noted to suffer from a high degree of depressive comorbidity.

We present a case in which nefazodone was successfully used to treat panic disorder, not associated with major depression, in a patient unable to tolerate the effects of an SSRI.

Case report. Mr. A, a 27-year-old male, had a history of panic disorder with agoraphobia that caused significant distress in his occupation. At the time of his initial presentation, he was experiencing 4 or 5 panic attacks per week, he had stopped operating his automobile, and he experienced distress associated

with leaving home. His wife accompanied him everywhere in order to call for assistance, if needed, during a panic attack. A trial of paroxetine, 10 mg q.d., and clonazepam, 0.5 mg b.i.d., was begun with the goal to titrate paroxetine slowly upward by 10 mg a week and taper off clonazepam in 2 to 3 weeks. In addition to the medications, the patient started a course of cognitive-behavioral therapy, which lasted for 16 sessions. The therapy initially focused on relaxation training paired with gradual, imaginative presentations of a hierarchy of feared situations. Therapy then emphasized direct in vivo exposure to the situation that originally resulted in Mr. A's initial panic attacks.

Mr. A did well, attributing his progress to what he had done in his cognitive-behavioral therapy sessions and to his medication. He initially experienced loose stools, believed to be a side effect of the paroxetine, but continued his drug therapy, as the panic attacks had decreased to 1 per week at the end of 3 weeks of treatment. Paroxetine had been increased to 30 mg daily, and clonazepam treatment had been discontinued. He was able to return to his job, performing at the same high level that he had before his panic disorder began. He was also driving again unaccompanied by his wife. At each subsequent appointment over the next 8 weeks, despite specific inquiry, Mr. A denied any sexual dysfunction. He reluctantly admitted to retrograde ejaculation, which was interfering in his marriage. At that point, a decision was made to slowly taper the paroxetine and initiate nefazodone at a low dose. Nefazodone was selected principally because it is associated with few or no sexual side effects.[5] The patient started at 50 mg b.i.d., and paroxetine was tapered by 10 mg per week.

Mr. A was able to tolerate the change, but, 3 days after nefazodone was initiated, he experienced visual trails, which he described as "laser lights" or "falling stars" that lasted a few hours. This adverse effect eventually terminated on the seventh day after starting nefazodone. The dose was increased slowly (50 mg/week) to 200 mg b.i.d. with no further side effects. Mr. A has denied any sexual dysfunction, confirmed by his wife, and has not required concurrent benzodiazepine treatment. He remains panic free at 6 months, continues to use self-relaxation techniques when under stress, and is fully integrated into the work place.

Although this is just one case demonstrating the usefulness of nefazodone in treating panic disorders, we remain cognizant that it is equally important that the patient be treated with cognitive-behavioral therapy, as well as medication. We also remind clinicians that although the use of nefazodone can be added to the list of treatment options available to clinicians, placebo response rates can be high.[6] We agree with Dr. Rosenbaum[7] that nefazodone shows promise and certainly merits further investigation in its use for the treatment of panic disorder.

The opinions and assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the U.S. Government, Department of Defense, Department of the Army, the Army Medical Department, or 82d Airborne Division.

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Gastroesophageal Reflux as a Possible Result of Clozapine Treatment

Sir: Stoner and colleagues provided interesting and what they called "encouraging" reports of 2 full-term infants born to mothers taking clozapine.[1] One 8-day-old infant had a seizure potentially due to clozapine, because the drug crosses the placenta. The same infant had evidence of gastroesophageal reflux, but diagnosis was uncertain owing to apparent concomitant gastroenteritis.

Our clozapine-treated patients commonly complain of heartburn that is worse when they are recumbent. Others[2] and we[3] have speculated that clozapine reduces esophageal motility. We strongly suspect that the signs of gastroesophageal reflux in the infant described by Stoner et al. were caused by clozapine and encourage evaluation for this adverse effect in patients taking the drug or infants born to women taking clozapine.

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