

### Careful Monitoring for Agranulocytosis During Carbamazepine Treatment

**Sir:** Schizoaffective disorder affects approximately 0.5% to 0.8% of people.<sup>1</sup> Mood stabilizers are an important component in the treatment of this disorder. Carbamazepine is a mood stabilizer that has been used alone and in combination with other mood stabilizers, antipsychotics, and antidepressants for the stabilization and maintenance treatment of schizoaffective disorder. Here, we report a patient who has been stable on carbamazepine treatment for 12 years and whose white blood cell counts (WBCs) have been decreasing over the last 2 years. Analysis of the risk/benefit ratio dictated continuing treatment with carbamazepine.

Agranulocytosis associated with the use of carbamazepine is well known. The collective incidence of thrombocytopenia, agranulocytosis, and aplastic anemia ranges from 1% to 2%.<sup>1</sup> Recommendations suggest discontinuation of carbamazepine with WBC less than 3000 mm<sup>3</sup>, absolute neutrophil count (ANC) less than 1500 mm<sup>3</sup>, or platelet count less than 100,000 per mm<sup>3</sup>.<sup>2</sup> No guidelines are available for patients who have a WBC that is very low but remains above the threshold discontinuation levels. Although carbamazepine treatment may be continued, closer monitoring may be warranted. The prognosis of schizoaffective disorder appears to more closely resemble that of schizophrenia than those of other mood disorders. Therefore, careful review of monitoring recommendations for the mood stabilizers, in this case carbamazepine, is extremely important to help assure positive outcomes for our patients.

**Case report.** Mr. A is a 50-year-old man who is seen in our clinic for schizoaffective disorder. The patient's diagnosis was based on DSM-IV-TR criteria<sup>3</sup> and has been present for over 30 years. He does not meet criteria for current alcohol or substance abuse or dependence. He was hospitalized every year for the first 10 years after his initial diagnosis and then every 2 years for the next 10 years. Board of Mental Health commitments initiated by his family prompted many of these hospitalizations. He has not had a hospitalization for the last 12 years, although he spent 9 years in a partial hospital program and was discharged 6 years ago. He had 1 suicide attempt during a hospitalization in 1978.

Mr. A's past medications have included lithium (with which he was treated for 25 years; he states he had 18 manic episodes during this time), thioridazine, and chlorpromazine. For the last 12 years, he has remained clinically stable on carbamazepine treatment. The patient's family psychiatric history is positive for bipolar disorder in his brother. His medical history is significant for hypercholesterolemia, obesity, and chest pain.

The patient is currently on disability and has little social support. He has never been married, has no children, and lives by himself.

He continues to display delusional thinking—current delusions include paranoia about military and CIA operations—as well as mild circumstantiality in his speech, but attributes the lack of hospitalization in the last 12 years to ongoing carbamazepine treatment.

Recent laboratory data (gathered in October 2005) have included WBC of 3000 mm<sup>3</sup>, platelet count of 128,000 per

mm<sup>3</sup>, and ANC of 1500 mm<sup>3</sup>. Since then, Mr. A's counts have begun to increase, but have remained at WBCs of 3000 to 3600 mm<sup>3</sup>. We entertained the option of switching his mood stabilizer, but he resisted, as he thought that he did best on carbamazepine treatment. After much discussion and weighing of the benefits and risks, our team has decided to continue the patient on carbamazepine treatment. Due to the high risk of infection and mortality caused by undiagnosed agranulocytosis, we have continued monitoring his complete blood counts with differentials on a monthly basis. We also monitor for symptoms such as sore throat, fever, or other symptoms indicative of agranulocytosis on a regular basis. He has not reported any of these symptoms, and his schizoaffective disorder has remained otherwise stable.

A decrease in WBC is thought to occur with carbamazepine due to the inhibition of colony-stimulating factor in the bone marrow. The coadministration of lithium, which stimulates colony-stimulating factor, can sometimes reverse the effects of carbamazepine.<sup>1</sup> One study<sup>4</sup> looked at the probability of psychotropic drugs causing blood dyscrasias. Not surprisingly, clozapine, at 0.18% of patients exposed, and carbamazepine, at 0.14% of patients exposed, were the 2 most likely to induce changes in WBC.<sup>4</sup> Leukopenia occurs transiently in about 10% and persistently in about 2% of carbamazepine-treated patients and typically develops within the first 3 months of treatment.<sup>5</sup> Importantly, carbamazepine is the second leading cause of agranulocytosis by a psychotropic medication,<sup>4</sup> yet strict guidelines do not exist for monitoring as they do for clozapine. Initially, the manufacturer of carbamazepine had extensive guidelines for monitoring for blood dyscrasias. However, due to the rarity of the blood dyscrasias, the guidelines were removed. It can be argued that because of the rapid onset of the abnormalities, daily laboratory checks would be needed, and this is impractical in almost all clinical settings. Much of the literature, therefore, focuses mainly on informing patients about the symptoms and signs of the blood dyscrasias to assist in early detection. These can include fever, sore throat, rash, and many others.<sup>6</sup>

Patients with a low leukocyte or neutrophil count before treatment may be at increased risk for carbamazepine-induced leukopenia or neutropenia. The most intense monitoring should be done for high-risk patients during the first 3 months of treatment, with the frequency being determined by results of each laboratory value.<sup>5</sup> Interestingly, discontinuation of therapy is usually not indicated unless symptoms are severe, persistent, or accompanied by infection. Leukopenia often reverses, even if carbamazepine treatment is continued. A severe risk of infection exists when the patient's neutrophil count falls below 500 mm<sup>3</sup>.<sup>7</sup>

In conclusion, careful clinical and hematologic monitoring on a case-by-case basis is the best way to recognize this life-threatening side effect.<sup>8</sup> Prompt reduction or withdrawal of carbamazepine is warranted on the basis of laboratory or clinical data. Administration of an adequate anti-infectious therapy can be necessary. Review of the literature cited above validates our choice to continue carbamazepine treatment in this patient. He has been educated on the signs and symptoms of the blood dyscrasias. We will continue monthly monitoring of his complete blood count until his blood counts return to a normal level, with the hope of recognizing any abnormality as early as possible.

If it becomes impossible to keep him on carbamazepine treatment, we postulate that a comparable medication to use would be oxcarbazepine due to its similar chemical structure.

*The authors report no financial or other relationship relevant to the subject of this letter.*

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## Mirtazapine-Induced Nightmares

**Sir:** Mirtazapine is classed as a noradrenergic and specific serotonergic antidepressant (NaSSA). It acts by blocking  $\alpha_2$  receptors on noradrenergic neurons and enhancing norepinephrine release.<sup>1</sup> Increased levels of norepinephrine act on  $\alpha_1$ -adrenoceptors on serotonergic cell bodies, increasing serotonergic firing.<sup>1</sup>

Nightmares occur only in rapid eye movement (REM) sleep. Most antidepressants suppress REM sleep; hence, nightmares are not a commonly reported side effect of therapy with antidepressants. We report the first ever case, to our knowledge, of a patient who developed severe nightmares on initiation of therapy with mirtazapine, which necessitated stopping the drug.

**Case report.** Mr. A, a 52-year-old white man, presented in 2006 with depressive symptoms including low mood, poor sleep and appetite, loss of weight, hopelessness, and fatigue. Because of his symptom profile, he was started on mirtazapine, 15 mg at night. One day later, he reported vivid nightmares of being murdered and his body being cut up. These nightmares woke him from sleep and left him feeling very scared and upset. He recalled that he had been treated with mirtazapine 2 years ago and it had to be discontinued because of similar distressing nightmares. After 4 days of therapy and experiencing nightmares every night, he requested that the medication be stopped.

The nightmares disappeared 1 day after cessation of mirtazapine. He denied ever experiencing such distressing nightmares in the past, except when he was taking mirtazapine. His only other concurrent medication was hydroxymorphone.

The temporal relationship between the initiation of treatment with mirtazapine and onset of nightmares and their disappearance with discontinuation of the drug, and also their occurrence during a previous episode of mirtazapine treatment, suggest a causal etiology.

Most antidepressants suppress REM sleep.<sup>2</sup> Mirtazapine has been shown to increase REM sleep even with acute administration, i.e., at 2 days.<sup>3</sup> It has also been shown to increase total sleep time, sleep efficiency, and stage 2 and slow wave sleep. These effects persisted after 5 weeks of treatment.<sup>3</sup>

Vivid dreams and nightmares have been reported with other antidepressants that increase REM sleep, such as bupropion.<sup>4</sup> It is possible that mirtazapine increased REM sleep in this patient, which may have induced nightmares. Clinicians should be aware of this side effect, as it can potentially affect treatment adherence.

*The authors report no financial affiliations relevant to the subject of this letter.*

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## Crohn's Disease Mimicking Bulimia Nervosa

**Sir:** Medical literature has recognized that the signs and symptoms of eating disorders and gastrointestinal diseases can be similar.<sup>1</sup> McClain et al.<sup>1</sup> described many gastrointestinal diseases that can simulate an eating disorder. We report a case of a woman with Crohn's disease mimicked bulimia nervosa.

**Case report.** In 2002, Ms. A, a 25-year-old white woman with a past medical history of eating disorder, was referred to psychiatry for a secondary consultation. Her history of present illness included recurrent, episodic vomiting with unintentional weight loss of approximately 25 pounds during 2001. Laboratory studies and computed tomography scan of the abdomen

were unremarkable prior to referral. Her primary care doctor and prior gastroenterologist had diagnosed her with an eating disorder. Although the referral to psychiatry had been made, Ms. A presented to us on her own for a second gastrointestinal evaluation.

Upon presentation, Ms. A had symptoms of nausea, vomiting, and early satiety. She denied depression, distorted body image, and sleep disturbances. In addition, she denied melena, hematochezia, hematemesis, abdominal pain, and diarrhea. Physical examination revealed a thin woman weighing 100 pounds with a height of 66 inches. Laboratory examination showed a normal C-reactive protein and hematocrit. An upper endoscopy showed pyloric stricture, and biopsy samples showed noncaseating granulomas. The colonoscopy findings were normal. She was diagnosed with Crohn's disease, treated with pyloric dilation, and maintained with aminosalicylates and 6-mercaptopurine. Gradually, she was able to tolerate a regular diet and subsequently returned to her baseline weight.

There are a few reported cases<sup>2-4</sup> of Crohn's disease that present with gastroduodenal involvement. We report a rare case of duodenal Crohn's disease presenting with a pyloric stricture. The stricturing resulted in early satiety, recurrent vomiting, malnutrition, and weight loss. Several physicians, on the basis of her symptoms as well as her demographic as a young woman, diagnosed her with an eating disorder. However, endoscopic evaluation revealed pyloric stricture, and histologic samples showed noncaseating granulomas. The clinical presentation, endoscopic findings, and histologic evaluation were consistent with Crohn's disease.<sup>5-7</sup>

Recurrent vomiting and unhealthy weight loss are symptoms that can describe both bulimia nervosa and duodenal

Crohn's disease. Medical literature has suggested the idea that gastrointestinal disease can masquerade as an eating disorder.<sup>1</sup> Our patient had Crohn's disease that presented like a psychiatric disorder. When evaluating a young woman for eating disorder, physicians should include the possibility of Crohn's disease as well as other gastrointestinal diseases in the differential diagnoses.

*The authors report no financial or other affiliation relevant to the subject of this letter.*

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