

Letters to the Editor

Rebound Psychiatric and Physical Symptoms After Gabapentin Discontinuation

Sir: Serotonin reuptake inhibitors (SRIs) offer the most effective pharmacologic treatment for obsessive-compulsive disorder (OCD). Since few patients have a complete response, there is a compelling need for augmentation strategies.¹ We initiated a pilot study to evaluate whether gabapentin might be a useful augmenting agent in a group of patients with OCD (Corá-Locatelli G, Greenberg BD, Martin JD, et al. 1997. Unpublished data). Gabapentin is a neutral gamma-aminobutyric acid (GABA) analog, which, in general, has few side effects and, overall, appears to be a safe, easy-to-titrate, well-tolerated drug in patients with seizure disorders. Its use in other neuropsychiatric disorders is currently under investigation. Gabapentin does not appear to cause dependence or other long-term side effects.² Based on encouraging preliminary results, we are currently conducting a placebo-controlled trial to evaluate the possible efficacy of gabapentin augmentation.

We report the appearance of rebound psychiatric and physical symptoms after discontinuation of gabapentin augmentation in a group of patients with OCD and comorbid anxiety and mood disorders who were receiving ongoing, long-term treatment with the SRI fluoxetine.

Case report. Five patients with OCD (3 with comorbid mood disorder and 4 with anxiety-related physical symptoms: spastic colon, headaches, nonspecific gastrointestinal symptoms) were on a stable dose of fluoxetine (mean dose = 70 mg/day; range, 50–80 mg/day) prior to the addition of gabapentin (mean dose = 3060 mg/day; range, 900–3600 mg/day). All patients had experienced a mild to moderate improvement of OCD, anxiety, depression, and sleep during gabapentin augmentation. All patients abruptly discontinued gabapentin: 2 ran out of medication, 1 decided that gabapentin was adding little benefit, and 2 discontinued blinded gabapentin and went on to the next phase of a placebo-controlled clinical trial. Within the following week (Days 2 to 7), all 5 patients reported the reappearance of their baseline symptoms: increased anxiety, obsessional thinking, depression, and decreased sleep. These symptoms were markedly more pronounced and intense than before gabapentin was added to SRI treatment. Two patients were unable to continue working because of severe OCD, anxiety, depression, and somatic symptoms. These 2 patients reported the recurrence of severe migraine headaches, 1 reported a relapse in spastic colon-related diarrhea, and 2 reported increased, nonspecific gastrointestinal distress. Although rebound OCD symptoms were not quantified in the beginning, all 5 patients contacted us prior to their pre-scheduled follow-up appointment and reported their OCD symptoms as the worst they had ever experienced. Gabapentin treatment was restarted in 4 of these patients, and these baseline symptoms subsided within the next week.

To our knowledge, there appear to be no prior reports of rebound psychiatric symptoms after gabapentin discontinuation in other patient groups. These cases suggest that OCD patients who

had a mild to moderate therapeutic response to gabapentin augmentation of fluoxetine treatment may have an acute reappearance of OCD, anxiety, and depression if gabapentin treatment ceases abruptly. Gabapentin is a GABA analog that increases GABA levels and does not interact with GABA or benzodiazepine receptors.^{3,4} The abrupt decrease in GABA levels may account for the appearance of these rebound symptoms, which are reminiscent of the symptoms that may occur after short-acting benzodiazepines are discontinued. We propose that clinicians consider a slow taper of gabapentin prior to discontinuation. Likewise, increasing gabapentin doses temporarily will probably relieve these rebound symptoms. Further controlled studies are needed to establish the mechanism and the clinical implications of this apparent discontinuation syndrome.

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Elevated Plasma Clozapine Concentrations After Phenobarbital Discontinuation

Sir: Clozapine, an atypical antipsychotic drug, is used mainly for treatment-resistant schizophrenia. Its metabolism is quite complex and involves a number of human cytochrome P450 enzymes and flavin-containing monooxygenases.^{1,2} Among them, cytochrome P450 1A2 (CYP1A2) appears to be the main enzyme responsible for the metabolism of clozapine.^{1,2} However, other isozymes, including CYP3A3/4, might also partially mediate clozapine's disposition.^{1,2} Numerous inhibitors of cytochrome P450 enzymes, e.g., cimetidine,³ erythromycin,^{4,5} and several serotonin selective reuptake inhibitors,⁶ can therefore elevate plasma clozapine levels. Conversely, 2 anticonvulsants, carbamazepine⁷ and phenytoin,⁸ could decrease plasma clozapine levels via the induction of the P450 system. It is noteworthy that a change in clozapine concentration affects the drug's efficacy and side effects.^{2,9,10} To our knowledge, the drug interaction between clozapine and phenobarbital, another anticonvulsant, has not yet been reported. The present case report demonstrates elevated plasma concentrations of clozapine after

phenobarbital was discontinued in a clozapine-treated schizophrenic inpatient.

Case report. Mr. A, a 26-year-old Chinese nonsmoker, was hospitalized for refractory schizophrenia. After having failed adequate trials of 3 classes of traditional antipsychotic drugs, he was given clozapine alone. Compliance was carefully monitored by a nurse. The dosage of clozapine was titrated to 300 mg/day in 3 weeks and then increased over the next 9 months to 600 mg/day (300 mg b.i.d.). He responded well to the dosage. However, a seizure occurred 10 days after the maximum dose was reached. Thus, phenobarbital 60 mg/day was coadministered to prevent further seizures. Owing to Mr. A's stable mental status over the next 2 months, the dose of clozapine was then tapered down to 400 mg/day over another 2 months.

Mr. A was then transferred to our study group for the monitoring of plasma levels of clozapine and its major metabolites, desmethylclozapine and clozapine-*N*-oxide. The steady-state plasma concentrations of clozapine, desmethylclozapine, and clozapine-*N*-oxide, 1 month after 400 mg/day of clozapine was used regularly, were 346 ng/mL, 241 ng/mL, and 65 ng/mL, respectively. Phenobarbital was then gradually tapered off and discontinued over the next month. Two weeks and 4 weeks respectively, after phenobarbital discontinuation, the plasma levels of clozapine, desmethylclozapine, and clozapine-*N*-oxide were elevated to 608 ng/mL and 602 ng/mL, 253 ng/mL and 280 ng/mL, and 87 ng/mL and 96 ng/mL, respectively. Plasma concentrations of clozapine and its 2 metabolites were measured simultaneously using high-performance liquid chromatography with ultraviolet detection as described in detail by Weigmann and Hiemke,¹¹ with some modifications.¹² The intraassay and interassay coefficients of variation were 7.9% to 14.7% at 50 ng/mL for clozapine and its metabolites. The lower limit of detection for clozapine was 1 ng/mL and for the metabolites was 2 ng/mL. All samples were assayed in duplicate. Following phenobarbital withdrawal, moderate sedation and drowsiness appeared without other clinically significant changes. Mr. A has remained seizure free ever since phenobarbital was first administered.

In the present patient who took phenobarbital to prevent possible clozapine-related seizures, plasma clozapine levels were markedly elevated (around 75% higher) after the discontinuation of the barbiturate. This fluctuation in plasma level might result from the potential clozapine-phenobarbital pharmacokinetic interaction. It has been demonstrated that phenobarbital can induce multiple P450 isozymes in rats¹³ and at least CYP1A2¹⁴ and CYP3A3/4¹⁵ in humans. It is also possible that the slow baseline clozapine metabolism (and the resultant higher plasma clozapine levels) in Chinese persons¹⁶ make this ethnic group more vulnerable to the action of a P450 enzyme inducer. On the other hand, 4 weeks after phenobarbital withdrawal, the desmethylclozapine level remained relatively constant (16% higher), whereas the clozapine-*N*-oxide level rose moderately (48% higher). It is currently difficult to explain this phenomenon because the dispositions of clozapine, desmethylclozapine, and clozapine-*N*-oxide are complex and not fully understood.^{1,2,17} For example, desmethylclozapine might be further metabolized to a hydroxylated metabolite via an unidentified enzyme,¹⁷ and clozapine-*N*-oxide could possibly be converted back to its parent compound.^{1,17,18}

Although clozapine's metabolites have been reported as pharmacologically inactive,¹⁹ recent evidence suggests that clozapine and desmethylclozapine are both potent 5-HT_{1C} receptor antagonists and have a similar affinity for D₂ and 5-HT₂

receptors.²⁰ In contrast, the *N*-oxide metabolite appears to be without significant pharmacologic activity.²⁰ Due to the somewhat stable desmethylclozapine levels in the patient described in this report, the side effects that emerged after the discontinuation of phenobarbital might be largely attributable to the elevation of plasma levels of clozapine itself. A drawback of this case study is quite evident: an initial pre-phenobarbital plasma clozapine-only level was unavailable. Further studies to demonstrate the clozapine-phenobarbital interaction are needed. This case suggests that caution be exercised when withdrawing or tapering down phenobarbital in clozapine-treated patients. Elevated plasma clozapine concentrations and concentration-related adverse drug effects, such as dizziness, sedation, or potential seizures, might occur.

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Can Bruxism Respond to Serotonin Reuptake Inhibitors?

Sir: Bruxism, the nonfunctional grinding and/or clenching of teeth, is thought to be a highly prevalent disorder.¹ Nocturnal bruxism has been classified as a parasomnia,² and patients may conceivably have sufficiently severe symptoms to meet DSM-IV criteria for stereotypic movement disorder. While both psychological (e.g., stress) and dental (e.g., malocclusion) factors have in the past been hypothesized to result in bruxism, its etiology remains poorly understood.

There is some evidence that specific neurobiological factors play a role in mediating bruxism.³ Bruxism appears more prevalent in children with brain damage and in mentally retarded persons.⁴ Bruxism has been reported in association with the use of amphetamines and L-dopa, as well as with chronic exposure to dopamine blockers.^{4,5} The serotonin system has been implicated in preclinical models of repetitive behaviors including repetitive chewing.⁶ While there is evidence that stereotypic movement disorder may respond to serotonin reuptake inhibitors (SRIs),^{7,8} these agents have in fact been reported to exacerbate bruxism.^{9,10}

We wish to report 2 patients treated with serotonin reuptake inhibitors, both of whom subsequently reported as an incidental observation a decrease in nocturnal bruxism.

Case 1. Ms. A, a 23-year-old woman who presented with violent obsessions and checking compulsions, clearly meeting DSM-IV diagnostic criteria for OCD, responded well to treatment with paroxetine 40 mg daily. During the course of the treatment, she noted that her husband had reported a significant decrease in her teeth grinding while she was asleep. This grinding had previously kept him awake and had also been diagnosed as a problem by her dentist. The response was maintained over the subsequent year of pharmacotherapy.

Case 2. Ms. B, a 61-year-old woman, presented with symptoms of a major depressive episode. She responded well to treatment with citalopram 20 mg daily. During the course of treatment, she reported that she no longer had nocturnal teeth grinding, which had been a problem for several years previously. She was certain of this because she no longer felt soreness in her jaw muscles on waking. The patient maintained this improvement during the subsequent months of pharmacotherapy.

It is unclear why SRIs had a different effect in our patients from that reported previously.^{9,10} Nevertheless, our data are consistent with previous work showing that more destructive bruxism is associated with REM sleep and that REM-suppressing tricyclic antidepressants may be useful in decreasing bruxism.^{4,11} It would be interesting to determine whether antidepressants also affect psychological variables that have been postulated to contribute to bruxism.¹² It seems arguable from our

patients' histories that the neurochemical basis of bruxism is a worthwhile subject for further study and that a trial of antidepressants may be considered in patients with bruxism, particularly where there is comorbid psychiatric illness or where severe symptoms fail to respond to other interventions¹³ for this condition.

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Article Commended

Sir: We wish to make it clear that we in no way intended to indict Dr. Leo's review of EPS in SSRI administration.¹ We rather were intending to point out the limitation of our own methodology² and the problems inherent to the literature. We indeed commend Dr. Leo for his excellent review of this subject.

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Possible Dose-Response Relationship for Risperidone in Obsessive-Compulsive Disorder

Sir: Stein and colleagues¹ described 8 patients with obsessive-compulsive disorder (OCD) previously refractory to serotonin reuptake inhibitor (SRI) treatment who substantially improved after treatment augmentation with risperidone. Although it is impressive that 37.5% of these subjects improved much to very much, Saxena and colleagues² made an even more dramatic report of clinically significant improvement in 67% of 21 SRI-refractory OCD patients after risperidone augmentation of the SRI. Caution is in order when comparing Stein and colleagues' retrospective case series with Saxena and colleagues' uncontrolled open trial, but it is striking that Saxena's group employed a risperidone dose more than twice that used by Stein's group (mean daily dose, 2.75 mg vs. 1.25 mg). Even though both groups reported favorable response to risperidone, the higher risperidone dose in Saxena and colleagues' study may contribute both to the higher response rate and to the higher rate of risperidone intolerance (23.8% vs. 12.5% in Stein and colleagues' cohort).

It is reasonable to use very low risperidone doses in supplementing SRI treatment for OCD, but it seems prudent to try risperidone doses above 2 mg daily for patients who remain treatment refractory. Finally, it is worth noting that none of Stein and colleagues' subjects had a history of comorbid tics. The limited data on augmentation strategies for refractory OCD with comorbid tics argue against risperidone addition and for haloperidol addition.^{2,3}

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Dr. Stein and Colleagues Reply

Sir: We appreciate the thoughtful observations of Dr. Baker. It seems clear, as we concluded in our paper, that there is a need for further controlled research to confirm the positive findings so far achieved in open trials of risperidone augmentation of serotonin reuptake inhibitors (SRIs) in obsessive-compulsive disorder (OCD) and to obtain information about optimal dosage and duration of risperidone.¹

Our OCD clinic has tended to use relatively low doses of risperidone in light of early reports suggesting that 1 mg/day of this medication was sufficient for augmentation,² in view of possible interactions between SRIs metabolized by CYP2D6 and risperidone (a number of our patients were, for example,

taking paroxetine), and also because one of the first patients in our clinic who was exposed to higher doses of the medication (4 mg/day) experienced onset of major depression as an apparent adverse effect.¹ More recent studies³⁻⁵ have, however, used relatively high doses of risperidone (mean, 2.75-3.6 mg/day) to augment certain serotonin reuptake blockers in OCD with good effect. Of note, though, there have also been recent reports indicating that risperidone at doses of 5 to 6 mg/day may exacerbate OCD symptoms in patients with schizophrenia.^{6,7} While there may well be, as Dr. Baker implies, a linear dose-response relationship for risperidone augmentation in OCD, controlled research in this area is needed to substantiate this and to determine optimal dosing with different SRIs.

Dr. Baker also states that the limited data on augmentation strategies for refractory OCD with comorbid tics argue against risperidone addition and for haloperidol addition. McDougle et al.⁸ did indeed find that haloperidol is useful in OCD patients with comorbid tics in a placebo-controlled study, while Saxena et al.³ found that a number of similar patients (N = 5) had a relatively poor response to risperidone. However, risperidone has also been reported to be useful in patients with tics in a growing number of studies.⁹⁻¹¹ Given the apparently favorable side effect profile of the atypical neuroleptics, there seems to be a good case for arguing that further controlled study of their use in treating OCD patients with comorbid tics is warranted.

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