References


Medication Withdrawal Symptoms in Obsessive-Compulsive Disorder Patients Treated with Paroxetine

Editors:

At the termination of a placebo-controlled clinical trial assessing the efficacy of paroxetine in the treatment of obsessive-compulsive disorder, unexpected and sometimes disabling medication withdrawal symptoms of lightheadedness and dizziness were noted in many of our subjects. Five (38.5%) of 13 subjects reported the onset of new adverse events during medication taper or within 2 to 14 days after their last dose. For the most part, these symptoms occurred within 1 to 3 days after withdrawal and differed from side effects accompanying the medication trial. The onset of these withdrawal symptoms often paralleled the resolution of preexisting medication side effects.

Case Reports

Patient 1. Mr. A, a 33-year-old man, reported dry mouth, sweating, headache, constipation, delayed orgasm, impotence, anxiety, and akathisia during treatment with paroxetine. Because of worsening akathisia, paroxetine was decreased from 60 to 50 mg. Because of lack of efficacy and adverse events, paroxetine was subsequently decreased to 20 mg at a rate of 10 mg every 3 to 4 days. After 17 days on 20 mg, paroxetine was discontinued. Three days later, Mr. A reported dizziness that lasted for 1 week. The dizziness resulted in bedrest and absence from work for 3 days.

Patient 2. Mr. B, a 41-year-old man, was treated with 40 mg of paroxetine for over 3 weeks. He then requested study termination because of a lack of efficacy, constipation, and difficulty with appointment scheduling. Paroxetine was tapered as follows: 30 mg for 4 days, 20 mg for 4 days, 20 mg every other day for 6 days, and finally discontinuation. Ten days after his last dose, he reported severe dizziness and "feeling close to blacking out." Dizziness remitted abruptly 1 week later when fluoxetine, 20 mg, was begun.

Patient 3. Mr. C, a 24-year-old man, was titrated up to 60 mg of paroxetine over a 2-week period and remained on this dose for 13 weeks. During the trial, he reported headache and insomnia. Because of a lack of efficacy, paroxetine was tapered to 30 mg for 10 days and then stopped. Two days later, the patient reported lightheadedness and "feeling faint," both of which lasted for a little over 2 weeks.

Patient 4. Mr. D, a 37-year-old man, was titrated up to 60 mg of paroxetine over 23 days and remained on this dose for 19 weeks. During this time, he reported headache, constipation, and initial insomnia. These adverse events resolved within 4 to 5 weeks on 60 mg of paroxetine. Because of a lack of efficacy, paroxetine was tapered by 10 mg every 4 days until a dose of 20 mg was reached. He then took 20 mg every other day for 1 week before discontinuing paroxetine. Dizziness, nausea, paresthesias, and headache accompanied the taper to 20 mg every other day and lasted 2 weeks before resolving.

Patient 5. Mr. E, a 38-year-old man, was increased to 60 mg of paroxetine over a 4-week period and remained on this dose for 5 months. Because of a lack of efficacy and adverse events (decreased libido and delayed ejaculation), he was abruptly withdrawn from the medication. Decreased libido and delayed ejaculation resolved 1 week after medication discontinuation; however, the day after stopping paroxetine, he reported the onset of lightheadedness and dizziness that lasted for 4 days.

Discussion

These case reports document the previously unreported occurrence of dizziness accompanying paroxetine withdrawal in approximately one-third of our obsessive-compulsive disorder patients. Paroxetine has a much shorter plasma half-life (20 to 24 hours) than the previously marketed serotonin-selective reuptake inhibitor (SSRI) fluoxetine (half-life, 7 to 15 days). Sertraline, another SSRI, has a half-life similar to that of paroxetine (approximately 25 hours); its primary metabolite, desmethylsertraline, is also an SSRI, but it is 5 to 10 times less potent than the parent compound and has a half-life of approximately 66 hours. Paroxetine apparently has no active metabolites. A recent report documents a withdrawal reaction following abrupt sertraline discontinuation in one patient. A computerized literature search did not locate any previous reports of withdrawal syndromes associated with paroxetine. Given paroxetine's short half-life and absence of active metabolites, however, we are unable to explain the long delay in onset of dizziness in patient 2. Future studies need to monitor drug levels in blood as a function of the emergence and resolution of withdrawal symptoms.

The literature documents that the withdrawal of tricyclic antidepressants precipitates syndromes attributable to cholinergic rebound in discrete areas of the brain or autonomic nervous system. Aside from its serotoninergic effects, paroxetine does not significantly inhibit the reuptake of other neurotransmitters or act on their receptors. It is of interest that in patient 2, the addition of fluoxetine abruptly stopped the withdrawal effects of paroxetine.

Given the significant rate of occurrence and potential sever-
Response to Anticonvulsant Substitution Among Refractory Bipolar Manic Patients

Editors:
Approximately 20 to 40% of patients with bipolar affective disorder do not respond, only partially respond, or cannot tolerate lithium therapy. This figure becomes higher for certain subpopulations, who are often described as "rapid cyclers," "mixed," "complicated," "dysphoric," or "atypical." High dropout rates have also been shown to occur during long-term lithium treatment. As a result, only a minority of patients may actually remain on successful prophylaxis for many years. In effect, lithium prophylaxis is not as effective as might be thought. Such failures contribute to the high incidence of recurrent manic syndromes and the poor outcome seen in bipolar patients.

With the recognition that certain anticonvulsant drugs can have psychotropic effects, we now have additional options for the pharmacologic management of bipolar illness. The efficacy of these agents may derive from their actions on γ-aminobutyric acid systems. Both double-blind and uncontrolled studies indicate that carbamazepine, a tricyclic compound, can be effective in the treatment of refractory mania and can also provide additional benefit for long-term prophylaxis and perhaps for the treatment of depression. Although controversial as to the specificity of action, Chouinard and colleagues report that clonazepam, a benzodiazepine derivative, can be a useful compound in the treatment of acute mania. The latest addition to this armamentarium is valproate, a simple branched fatty acid currently being investigated in the United States, following a substantial European experience dating back to the 1960s. In a recent placebo-controlled, double-blind study, Pope and colleagues found valproate to be an effective alternative treatment for patients who were not responsive to lithium.

There is a wide individual variation in response to specific anticonvulsant medications among epileptic patients. Given the different mechanisms of action of these agents, a differential clinical response could also be expected in bipolar patients. This report addresses the possibility by reporting on the substitution of valproate in 9 patients and carbamazepine in 1 patient among 10 patients who were not responsive or were only partially responsive to lithium, an adjunctive anticonvulsant agent.

Methods
Patients from whom consent was obtained were identified in the inpatient and ambulatory services of a medical school–affiliated municipal teaching hospital. The population contains a large number of chronically ill patients from a low socioeconomic group. We identified patients with bipolar spectrum disorder who either did not respond well to treatment after adequate trials of lithium and an anticonvulsant agent or could not tolerate lithium and were treated unsuccessfully with an anticonvulsant agent without lithium. Because the general augmentation practice at the time had been to use primarily carbamazepine or clonazepam, this study also afforded an opportunity to focus on the clinical effect of substituting valproate for the former agents. We also include one patient who was changed over to carbamazepine after a poor response to valproate. Ten cases were so identified.

Liver function tests and a complete blood count were performed at the start of valproate therapy and at regular intervals afterwards. Divalproex sodium, 250 to 500 mg twice daily, was administered during the first 2 days. Dosages were adjusted upward in increments of 250 mg/day until trough serum levels were within a range of 50 to 110 μg/ml.