

# Letters to the Editor

## Reboxetine Treatment of Depression in Parkinson's Disease

**Sir:** The efficacy and tolerability of reboxetine, a norepinephrine reuptake inhibitor, have been shown in patients with major depressive disorder or dysthymia.<sup>1</sup> This novel antidepressant shows negligible effects on psychomotor and cognitive function<sup>2</sup> and may be especially effective in improving negative self-perception and lack of motivation toward action.<sup>3</sup> Depression occurs frequently in Parkinson's disease and appears to be associated with greater frontal lobe dysfunctions, including reward and motivational systems, and greater involvement of dopaminergic and noradrenergic systems than in nondepressed Parkinson's patients.<sup>4</sup> We report for the first time reboxetine treatment of depression in Parkinson's disease after prior treatment with amitriptyline and fluoxetine was ineffective and accompanied by intolerable side effects.

**Case report.** Ms. A, a 68-year-old white woman, was treated by her neurologist with levodopa (325 mg/day) for Parkinson's disease, which had developed 2 years earlier. Motor symptoms, including more right-sided rigidity, akinesia, and gait instability, were satisfactorily controlled. She had no history of previous psychiatric disorders or prior psychopharmacologic treatment. Gradually, Ms. A developed depressive symptoms, including reduced appetite and weight loss, physical and social anhedonia, terminal insomnia, and negative self-perception, without changes in motor symptoms. Despite treatment with amitriptyline, up to 100 mg/day over a period of 6 weeks, in addition to levodopa, she was admitted to our clinic because of suicidal ideation and increasing deficits in concentration and short-term memory. When amitriptyline was tapered because of lack of efficacy and intolerable side effects, cognitive deficits and other anticholinergic effects declined. While keeping levodopa at a stable dosage, treatment with fluoxetine (up to 40 mg/day) was initiated, and mood, cognitive functions, and sleep improved moderately. However, 4 weeks later, Ms. A still suffered from depression that included increasing weight loss, anhedonia, social withdrawal, and inability to perform her daily activities, but no cognitive impairment. In addition, right-dominating rigidity and cogwheel phenomena in upper and lower extremities had increased. Motor phenomena, including rigidity, declined after fluoxetine was stopped.

The novel antidepressant reboxetine was started with a daily dosage of 1 mg, which was gradually increased to 4 mg. Because no motor symptoms were apparent, the dosage of levodopa was not altered. Initially, zolpidem was prescribed for problems with sleep. Transient sweating and feelings of slight agitation disappeared after 3 weeks. While dosages of levodopa and reboxetine were kept stable, Ms. A's mood elevated, her negative self-perception improved, her appetite increased, and she reported to actually enjoy her meals for the first time since the onset of depression. Neither side effects affecting gastrointestinal functions or motor performance nor changes in blood count, electrocardiogram, or electroencephalogram were found.

Reboxetine (4 mg/day) and levodopa (325 mg/day) were continued at stable dosages, and Ms. A's social functioning increased. Three months later, Ms. A was socially active again and able to perform her daily activities.

Good theoretical and clinical reasons exist to consider reboxetine for treatment of depression in Parkinson's disease, including pharmacologic specificity of effects and low incidence of side effects. Currently, evidence is insufficient to warrant the recommendation of reboxetine in the routine care of depression in Parkinson's disease patients. However, on the basis of this case report, the assumed effects of reboxetine on motivation toward action and social functioning, and the established noradrenergic mechanisms involving reward and motivational systems in depression of Parkinson's patients, we believe further studies to investigate the effect of reboxetine on depressive symptoms in Parkinson's patients are warranted.

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## Olanzapine-Induced Neutropenia in Patients With History of Clozapine Treatment: Two Case Reports From a State Psychiatric Institution

**Sir:** Olanzapine is an atypical antipsychotic that is similar in structure to clozapine, but has not been associated with hematologic adverse effects until recently.<sup>1,2</sup> Two case reports from different institutions described patients who experienced agranulocytosis<sup>1</sup> or neutropenia<sup>2</sup> while receiving olanzapine and had previously received clozapine during the course of their illness. In the first patient report, 5 months had passed between clozapine and olanzapine therapy, whereas only 5 days had passed between administration of the 2 agents in the second report. We present 2 patients whose white blood cell (WBC) counts fell while receiving olanzapine therapy after having been previously treated with clozapine. In the first patient, the time period between clozapine therapy and olanzapine therapy was 3

years, and in the second patient, the time period between the 2 medication treatments was 5 days.

**Case 1.** Mr. A, a 48-year-old black man, had a diagnosis of schizoaffective disorder (bipolar type), chronic paranoid schizophrenia, and schizoid personality disorder (DSM-IV criteria). He had been maintained on clozapine, 550 mg/day, for over 1 year with a WBC count that consistently oscillated between  $4.0$  and  $6.0 \times 10^3/\text{mm}^3$  over the course of the year. (Mr. A had been monitored weekly after a single incident in which his WBC count fell below  $4.0 \times 10^3/\text{mm}^3$ , but returned to levels between  $4.0$  and  $6.0 \times 10^3/\text{mm}^3$ .) However, Mr. A's clozapine treatment was discontinued after he had 2 consecutive absolute neutrophil counts (ANCs) that fell below 1100 cells/ $\text{mm}^3$ .

On discontinuation of clozapine, Mr. A's WBC count began to return to normal levels, and after 11 days without receiving clozapine, it had risen to  $7.3 \times 10^3/\text{mm}^3$ . At this time, olanzapine therapy was initiated at 10 mg/day and was rapidly titrated to 30 mg/day over the course of 2 weeks. During this time, Mr. A's WBC count was monitored every 5 to 7 days, since it is necessary to monitor WBC counts closely for at least 4 weeks after the discontinuation of clozapine therapy.<sup>3</sup> Within 1 week of starting olanzapine, 15 mg at bedtime, his WBC count had fallen slightly to  $5.5 \times 10^3/\text{mm}^3$ . At this time, Mr. A's WBC count was being evaluated every other day during the olanzapine dose titration. Within 1 week, his dose of olanzapine had been titrated from 15 mg/day to 30 mg/day. The first WBC count drawn while he was receiving 30 mg/day of olanzapine revealed that his WBC count had fallen to  $4.8 \times 10^3/\text{mm}^3$ , with an ANC of 974 cells/ $\text{mm}^3$ . Olanzapine was immediately discontinued, and Mr. A's WBC count slowly began to return to normal levels over the next 3 days: 4.8, 4.9, to  $5.2 \times 10^3/\text{mm}^3$ . His WBC count remained stable, and he was not rechallenged with olanzapine. Currently, he is being treated with the traditional neuroleptic thiothixene for his psychiatric condition.

**Case 2.** Mr. B, a 60-year-old black man with a diagnosis of chronic undifferentiated schizophrenia (DSM-IV criteria), had not received clozapine since 1994. Clozapine discontinuation was secondary to gallbladder surgery and not related to hematologic events. However, during clozapine therapy, his WBC counts consistently ranged from  $4.0$  to  $6.0 \times 10^3/\text{mm}^3$ , and on occasion, fell below  $4.0 \times 10^3/\text{mm}^3$ . Three years later, in 1997, Mr. B had been stabilized on olanzapine therapy at a dose of 30 mg/day for approximately 10 months. Owing to elevated blood glucose levels and weight gain, he was taken off olanzapine therapy, and a trial of quetiapine was begun, which failed to show any therapeutic benefit. Owing to his history of a robust response to olanzapine, olanzapine was reinstated with careful weight and blood monitoring. Mr. B was maintained on olanzapine, 20 mg/day, for 17 months. However, his WBC count declined to  $3.1 \times 10^3/\text{mm}^3$ , with an ANC of 1023 cells/ $\text{mm}^3$  (for a clinical diagnosis of neutropenia,  $\text{ANC} \leq 1500$  cells/ $\text{mm}^3$ ). It was decided to discontinue olanzapine. Five days later, Mr. B's WBC count and ANC had risen while off olanzapine treatment to  $4.5 \times 10^3/\text{mm}^3$  and 1986 cells/ $\text{mm}^3$ , respectively. Another trial of olanzapine, at a lower dose of 10 mg/day, was initiated with blood monitoring every other day. Within 1 week of receiving 10 mg/day of olanzapine, his WBC count fell slightly to  $4.0 \times 10^3/\text{mm}^3$ , with an ANC of 1860 cells/ $\text{mm}^3$ . Olanzapine was continued carefully with intensive blood monitoring. Mr. B's WBC count had returned to normal levels between  $4.0$  and  $5.0 \times 10^3/\text{mm}^3$  while he was stabilized on olanzapine, 10 mg/day.

These case reports further support the previously cited cases in that patients who have received clozapine in the past may be at an increased risk for neutropenia when treated with olanzapine.

The time frame and correlation between the 2 medications and risk for neutropenia remain unclear. However, a total of 7 patients now have experienced declines in WBC count when treated first with clozapine followed by olanzapine, regardless of the time interval in between. The decline in Mr. A's WBC count may have been due to residual clozapine effects (olanzapine was initiated within 4 weeks of clozapine discontinuation, which falls in the recommended monitoring period of WBC counts after the discontinuation of clozapine) or may have been entirely due to olanzapine. The possibility also exists that there was an additive insult of both the clozapine and olanzapine on Mr. A's bone marrow. One report<sup>4</sup> describes prolongation of clozapine-induced granulocytopenia with olanzapine in 3 patients. Whether or not this could explain what happened to Mr. A is unknown.

Our second case reported indicates that a relationship may exist between dose of olanzapine and degree of neutropenia. For Mr. B, a 3-year gap existed between treatment with clozapine and olanzapine. However, when he was being treated with clozapine, his WBC counts were in the lower range of normal. The clinical significance of this is not known, but it may be indicative of olanzapine's ability to decrease WBC counts in a patient already compromised owing to clozapine therapy. Mr. B's WBC count and ANC fell rapidly to  $3.1 \times 10^3/\text{mm}^3$  and 1023 cells/ $\text{mm}^3$ , respectively, at an olanzapine dose of 20 mg/day, whereas his WBC counts stabilized between  $4.0$  and  $5.0 \times 10^3/\text{mm}^3$  at an olanzapine dose of 10 mg/day. Whether or not this phenomenon is dose related or dose independent, continued and more intensive monitoring is needed in patients being treated with olanzapine who have been previously treated with clozapine. Monitoring these patients' WBC counts is especially important during the first 4 weeks after discontinuation of clozapine, when olanzapine therapy may be initiated, and during the early treatment with olanzapine in patients who have experienced drops in their WBC counts due to clozapine therapy.

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#### Venlafaxine Versus Sertraline for Major Depressive Disorder

**Sir:** The recent report by Mehtonen et al.<sup>1</sup> concludes that venlafaxine is superior in efficacy to sertraline in depressed psychiatric outpatients. A number of factors within the study suggest that their conclusion needs to be tempered. While the overall rates of discontinuation may have been comparable, the proportion of adverse events in the venlafaxine cohort was twice that of the sertraline cohort (16% vs. 7%), and of all

patients who discontinued medication treatment over the course of the study, the proportion of those discontinuing therapy in the first week with venlafaxine was also twice that of the sertraline group (8/16 = 50% vs. 3/12 = 25%, respectively). The proportion of adverse events for those discontinuing therapy in the first week of venlafaxine treatment was slightly greater than twice that for the sertraline group (6/8 = 75% vs. 1/3 = 33%, respectively).

In their analysis, the authors utilized a repeated-measures design, yet no repeated-measures analysis was performed. This type of analysis simultaneously assesses differences between groups over time and differences within points in time, appropriately controlling for type I errors. Was this the analysis that showed no meaningful differences between groups in Figure 1? It may be more appropriate and clinically meaningful to look at "response" and "remission" as study endpoints, but is it reasonable to examine them at only one point in time, such as week 8? Was there any analysis of like groups on remission/response to look for improvement with increased dose? Such questions are important because the study is not really a dose-response study, since the second dose was a doubling of the initial dose. More importantly, looking at Figures 2 and 3 and at high versus low dose within drug treatment groups, not just between the groups, there appears to be little difference in the venlafaxine group for response (81% vs. 83%) or remission (67% vs. 68%). The same is true for the sertraline group for response (67% vs. 68%) and remission (36% vs. 45%). The authors' data are suggestive, but more studies would be helpful.

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#### Adverse Events of Fluoxetine: Postmarketing Compared With Premarketing Clinical Trials

**Sir:** A prevalent perception exists among clinical pharmacologists and clinicians that the burden of adverse events is higher when a drug is utilized in the natural clinical environment than when used in premarketing clinical trials. The postmarketing study by Zajecka et al.,<sup>1</sup> which reported on the adverse events of fluoxetine, affords the opportunity to test this perception.

We compared the 6 most common adverse events reported in that study with the same adverse events as reported in the *Physicians' Desk Reference*<sup>2</sup> by utilizing the chi-square test. The results show that all events except 1 are significantly more common in the postmarketing study (Table 1). This is in spite of the fact that the patients in the premarketing study received 20 to 80 mg/day, whereas those in the postmarketing study received only 20 mg/day. The extent of the differences would have been even greater had the adverse events in the postmarketing study been solicited from the patients, as is usually done in premarketing clinical trials, rather than leaving the patient to spontaneously report these events. Conspicuously ab-

**Table 1. Percentage of Patients Reporting Adverse Events in Premarketing Versus Postmarketing Trials of Fluoxetine**

Adverse Event	Premarketing (N = 1730) <sup>a</sup>	Postmarketing (N = 299) <sup>b</sup>	$\chi^2$	p Value
Nausea	21.1	29.1	9.13	.005
Insomnia	13.8	22.4	15.90	< .001
Somnolence/ drowsiness	11.6	14.7	9.92	.003
Diarrhea	12.3	13.0	1.44	.70
Dizziness	5.7	13.0	22.5	< .001
Asthenia	4.4	12.0	30.6	< .001

<sup>a</sup>Data from Physicians' Desk Reference.<sup>2</sup>

<sup>b</sup>Data from Zajecka et al.<sup>1</sup>

sent from the premarketing and postmarketing lists of adverse events is sexual dysfunction, which was reported by fewer than 5% of the patients in the Zajecka et al. study.<sup>1</sup> This is probably the most common side effect of fluoxetine and other SSRIs, the most persistent, and the most important contributor to noncompliance with treatment. When solicited, this adverse event was reported by 34% of 160 outpatients receiving 20 to 40 mg of fluoxetine,<sup>3</sup> and in another study by 75% of 60 middle-aged men receiving 20 mg/day.<sup>4</sup>

It is worth noting that the study by Zajecka et al.<sup>1</sup> was supported by the company that markets fluoxetine and probably was conducted by some of the same centers and individuals that conducted the premarketing clinical trials, adding to the validity of comparing the 2 studies.

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#### Diagnosing Melancholia

**Sir:** In their recent article (1999, Supplement 20) reporting results from a double-blind randomized treatment of late-life depression, Mulsant et al.<sup>1</sup> found a lack of statistically significant difference between the rates of response to nortriptyline and paroxetine. The authors report that over 6 weeks of treatment, the tolerability of and response to therapeutic plasma drug levels were similar in their patients, irrespective of inpatient versus outpatient status or the presence or absence of melancholia. As the authors noted, these results are in discord with several reports including 2 multicenter, double-blind studies from the Danish University Antidepressant Group<sup>2,3</sup> and 1 from the New York State Psychiatric Institute (NYSPI).<sup>4</sup> In the search for an explanation of the marked difference in results, the authors state, "We found similar rates of response to nortriptyline and paroxetine when we restricted our comparison to inpatients

Table 1. DSM-III, DSM-III-R, and DSM-IV Criteria for Melancholia<sup>a</sup>

DSM-III	DSM-III-R	DSM-IV
<b>BOTH</b>	The presence of at least 5 of the following:	<b>EITHER</b> of the following, occurring during most severe period of the current episode:
Loss of pleasure in all or almost all activities AND Lack of reactivity to usually pleasurable stimuli (doesn't feel much better, even temporarily, when something good happens)	1. Loss of pleasure in all or almost all activities 2. Lack of reactivity to usually pleasurable stimuli (doesn't feel much better, even temporarily, when something good happens)	1. Loss of all pleasure in all or almost all activities 2. Lack of reactivity to usually pleasurable stimuli (doesn't feel much better, even temporarily, when something good happens)
AND at least 3 of the following:	3. Depression regularly worse in the morning 4. Early morning awakenings (at least 2 hours before usual time of awakening) 5. Psychomotor retardation or agitation (not merely subjective complaints) 6. Significant anorexia or weight loss (eg, more than 5% of body weight in a month) 7. No significant personality disturbance before first major depressive episode 8. One or more previous major depressive episodes followed by complete, or nearly complete, recovery 9. Previous good response to specific and adequate somatic antidepressant therapy, eg, tricyclics, electroconvulsive therapy, monoamine oxidase inhibitors, lithium	AND 3 (or more) of the following: 1. Distinct quality of depressed mood, ie, the depressed mood is perceived distinctly different from the kind of feeling experienced following the death of a loved one 2. The depression is regularly worse in the morning 3. Early morning awakenings (at least 2 hours before usual time of awakening) 4. Marked psychomotor retardation or agitation 5. Significant anorexia or weight loss 6. Excessive or inappropriate guilt

<sup>a</sup>Adapted from references 5–7, with permission.

or to patients with melancholic features, even though we used *the more stringent DSM-IV criteria for melancholia as opposed to the DSM-III and DSM-III-R criteria* [italics added] that were used in the NYSPI study.<sup>1(p19)</sup> The DSM-IV criteria represent the most current diagnostic criteria set for melancholia or endogenous depression; however, they are not the most strict, as the authors suggest.

Table 1 shows a side-by-side comparison of the 3 sets of criteria.<sup>5–7</sup> These definitions differ slightly in composition and diagnostic algorithm. DSM-III and DSM-III-R shared 6 symptoms, but 2 of the DSM-III criteria were eliminated and 3 new items were added in DSM-III-R. According to the DSM-III algorithm, the presence of anhedonia and lack of reactivity were required, together with at least 3 of the remaining 6 symptoms. In DSM-III-R, no symptoms were prerequisite for a diagnosis. Because there were no longer any necessary criteria and the pool of defining items increased from 8 to 9, with the minimum number of symptoms necessary remaining at 5, the prevalence of DSM-III-R melancholia was higher than DSM-III melancholia.<sup>8</sup>

In DSM-IV, which lists the same symptoms as the DSM-III set for melancholia, *either* anhedonia *or* unreactivity is required, together with at least 3 of the remaining 6 symptoms. Consequently, individuals that were identified as having melancholia according to DSM-III would most likely constitute a subset of individuals identified as having melancholia according to DSM-IV. This hypothesis is supported by a preliminary analysis of the data from our ongoing study. We found that of 536 patients diagnosed with a DSM-IV major depressive episode, 190 individuals met the DSM-IV criteria for melancholia and only 55 patients met the DSM-III criteria. Thus, 135 patients met DSM-IV but not DSM-III melancholia criteria. This finding is in clear contrast with the assertion by Mulsant et al.<sup>1</sup> that they have used the most stringent criteria for identifying depressed melancholics.

Most likely, this clarification will not help to explain major differences between the findings of Mulsant et al.<sup>1</sup> and those of other studies on the relative efficacy of tricyclics and selective serotonin reuptake inhibitors; however, readers should not be

misinformed about the diagnostic power of the DSM criteria. To our knowledge, the relative validity of the 3 DSM criteria sets for melancholia has not yet been explored. Nevertheless, it is evident that the DSM-IV definition of melancholia is definitely not the most stringent criteria set.

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