

# Letters to the Editor

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## Mirtazapine-Associated Palinopsia

**Sir:** Mirtazapine is a combined noradrenergic and selective serotonergic antagonist that is effective in the treatment of depression. The most common side effects of mirtazapine include dry mouth, drowsiness, sedation, increased appetite, and weight gain.<sup>1</sup> We report an unusual visual disturbance in one of our patients.

**Case report.** Ms. A, a 26-year-old woman with obsessive-compulsive personality disorder, sought treatment for her first major depressive episode, which was moderate and without psychotic features (DSM-IV). She had developed significant depressed and irritable mood, restlessness, increased anxiety, decreased appetite, and initial insomnia. She had a positive family history for depression and felt that the depressive symptoms had an association with a significant life transition. She received combined psychotherapy and pharmacotherapy. An initial trial of paroxetine was used in combination with clonazepam. Since paroxetine was ineffective, it was tapered. Mirtazapine was started at a dose of 15 mg at bedtime, while clonazepam was continued.

Ms. A had a moderate improvement of her insomnia, but, on the fourth day of treatment, developed the following side effect: As she watched her husband walk past her, she saw multiple afterimages of him as if he were leaving a visual trail. These afterimages were less color intensive than the normal visual image, slightly blurred, and faded away after 30 seconds to 1 minute. The phenomenon repeated itself with most moving objects and was generally more pronounced with objects in Ms. A's lateral visual fields. As the side effect occurred multiple times during a 24-hour period, she discontinued the mirtazapine, but continued the clonazepam. The visual effects disappeared within a day of the discontinuation of the mirtazapine.

She described the experience as anxiety-provoking and preferred not to restart the medication. She had no history of retinal disease, neurologic illness including seizures, migraine headaches, or cerebrovascular disease and had never used hallucinogens. She was not taking any other medications at the time of the event.

Palinopsia is a form of visual disturbance in which patients see an illusionary visual spread of moving objects. It is most commonly associated with structural posterior cerebral lesions, but has also been described in patients with diseases limited to the retina or the optic nerve.<sup>2</sup> In psychiatric practice, palinopsia is most commonly associated with the use of lysergic acid diethylamide (LSD),<sup>3</sup> nefazodone,<sup>4</sup> trazodone,<sup>5</sup> and risperidone.<sup>6</sup> Ours is the first case report of palinopsia that might be associated with mirtazapine. While we did consider neurologic illness, unreported substance use, and psychotic features of depression in our differential diagnosis and also considered a possible contributory effect of clonazepam, the correlation of the occurrence and disappearance of the palinopsia with the start and

withdrawal of mirtazapine suggests that mirtazapine might have been the trigger for the phenomenon. Trazodone, nefazodone, risperidone, and mirtazapine share antagonism at the 5-HT<sub>2</sub> receptor. LSD is a 5-HT<sub>2A</sub> and 5-HT<sub>2C</sub> agonist, and post-hallucinogen perception disorder might be related to reduced receptor stimulation. Our patient's visual disturbance lends support to the hypothesis that palinopsia is associated with 5-HT<sub>2</sub> antagonism or reduced 5-HT<sub>2</sub> receptor stimulation.

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## Type II Error and Antidepressants

**Sir:** We read with interest the study conducted by Weihs et al.,<sup>1</sup> which concluded that bupropion sustained release and paroxetine were similarly effective in elderly, depressed patients treated for 6 weeks. However, the authors' failure to observe statistical significance between interventions does not preclude the possibility of a clinically meaningful difference between the 2 agents. We suggest consideration of the possibility of a type II ( $\beta$ ) error or a falsely negative trial.

Negative trials are defined as studies that report no significant difference in outcome between the experimental and control groups. Analysis of published "negative" randomized controlled trials has shown that, owing to the small sample sizes used by investigators, there is often a surprisingly high probability of missing a clinically meaningful difference if one existed.<sup>2-5</sup> Therefore, when designing a clinical trial, researchers must report the power or estimate the appropriate sample size to minimize type II errors. The power indicates the ability to detect a true difference of clinical importance and is usually accepted at the 80% level. The sample size (N) is related to the  $\alpha$  error,  $\beta$  error, variance (the magnitude of dispersion around the sample mean), and the clinically relevant difference of interest.<sup>4</sup>

Among the 4 parameters, determination of the last is the most challenging component. The best estimate of a clinically relevant difference (i.e., that which would be important enough to change current practice) is based on previous studies or the clinical experience of the investigator.<sup>6</sup> In the aforementioned study,<sup>1</sup> the omission of statistical power or baseline values for the primary endpoints, for which power could be calculated retrospectively, allows for the possibility of false negative results.

Aside from omitting a power analysis, additional limitations restrict the ability to generalize the study's results to clinical practice. First, a study period extending beyond 6 weeks is needed because elderly patients with recurrent depression may exhibit higher relapse rates and a slower temporal course of depression.<sup>7</sup> Second, the only significant difference noted by the authors concerned the incidence of adverse events (somnolence, diarrhea) between the 2 interventions; however, they failed to mention whether concomitant medications (e.g.,  $\beta$ -adrenergic blocking agents, St. John's wort [*Hypericum perforatum*]) may have influenced patients' responses. Because the average older American uses 3 prescription drugs and 4 over-the-counter (OTC) drugs daily, and nursing home residents take 7 prescription drugs daily, it is important to take into account concomitant medications (e.g., herbals, OTC drugs, prescription drugs) used by these patients.<sup>8</sup>

In summary, the reader and clinician must be aware that negative trials may in fact be falsely negative. In the case of negative results (i.e., no statistically significant difference between treatment interventions), the investigators should present either the  $\beta$  error or the study's power ( $1-\beta$ ) to detect a clinically significant difference.

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#### Dr. Weihs and Colleagues Reply

**Sir:** We are grateful to Dr. Walker and colleagues for giving us the opportunity to reply to their letter regarding our article.<sup>1</sup> Their major concern with our report was the omission of a power analysis.

At the end of the study, the difference between the 2 treatment groups, bupropion sustained release (SR) and paroxetine, was approximately 1 point on the 21-item Hamilton Rating Scale for Depression (HAM-D), with a standard deviation of approximately 8 points. The number of patients needed to detect this difference with 80% power would be approximately 1000 per treatment group for a total of 2000 patients. In our study, with 50 patients per group, the power to detect a 1-point difference between the 2 treatment groups would be 9%. A 1-point difference in HAM-D score, however, can be questioned as being clinically relevant.

Antidepressant studies often aim to detect differences from placebo on the order of 3 points on the HAM-D. If 3 points is a clinically meaningful difference, the power to detect that difference in our study was approximately 45%. However, we know of no studies which suggest that the difference between these 2 approved antidepressants is 3 points. In fact, American Psychiatric Association treatment guidelines note similar rates of response for all antidepressant drugs.<sup>2</sup> Nevertheless, inclusion of the statistical power analysis clarifies the limits of these data to support that conclusion.

The conclusion that both treatments were similarly effective is difficult to argue against, even in light of the small sample size. The differences between the treatments at each visit for each of the efficacy measures is on the order of the standard error of the mean for each estimate (see the figures presented in the article<sup>1</sup>). We did not, nor can we, conclude that the treatments are clinically equivalent, a strict term that would require greater numbers of patients and equivalence testing methods. The point of this conclusion is valuable in examining the safety profiles of the 2 treatments, between which some statistically significant (albeit unadjusted for multiplicity) differences were seen. The 2 treatments, having similar antidepressant profiles, should be examined for similarities or differences in safety. Even though the study is not powered to detect a difference that is unlikely to exist, it was large enough to highlight some subtle differences in safety profiles.

Dr. Walker and colleagues also suggest that a study period longer than 6 weeks would be needed since "elderly patients with recurrent depression may exhibit higher relapse rates and a slower temporal course of depression." Although these patients may indeed exhibit higher relapse rates, this acute study was not designed to evaluate relapse rates in this population. Pivotal clinical studies of depression have often been of 6 weeks' duration<sup>3-25</sup>; studies designed to evaluate relapse rates are typically 6 months to 1 year in duration.<sup>26-29</sup> Moreover, although the elderly may have a "slower temporal course of depression," antidepressant response with both bupropion SR and paroxetine was unequivocal.

In response to the comment that "concomitant medications (e.g.,  $\beta$ -adrenergic blocking agents, St. John's wort [*Hypericum perforatum*]) may have influenced patients' responses," patients in the study were prohibited from taking any psychoactive medications, except chloral hydrate, during the study. Chloral hydrate was permitted for the first 14 days of the study; 3 patients in each treatment group used chloral hydrate during the study. No patient took St. John's wort during the study.

Drugs likely to affect the efficacy of paroxetine (drugs that induce the cytochrome P450 system enzymes that break down paroxetine such as anticonvulsants [e.g., carbamazepine, phenobarbital, phenytoin] or sedatives [e.g., barbiturates, meprobamate]) were prohibited during the study. As shown in Table 2 in our report,<sup>1</sup> the number of patients with concomitant illnesses at baseline was similar between the treatment groups, and, as would be expected, concomitant medication use was similar between the groups as well (bupropion SR, N = 45; paroxetine,

N = 46). Furthermore, patients taking antihypertensives, including  $\beta$ -adrenergic blocking agents, were to have been receiving the medication and on a steady dose for at least 6 months prior to study entry. Approximately the same number of patients in both treatment groups took  $\beta$ -adrenergic blocking agents (4 in the bupropion SR group and 3 in the paroxetine group). Finally, as stated in the Discussion of our article,<sup>1</sup> our adverse event findings were consistent with other reports, with references cited. The mechanism of action discussion in the same section helps to further explain our findings.

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#### Increase in Plasma Levels of Clozapine and Norclozapine After Administration of Nefazodone

**Sir:** Drug interactions can adversely affect the treatment of patients taking antipsychotic agents. Therefore, predictability of such interactions would be beneficial in avoiding unnecessary negative effects of drug therapy. However, predictability of drug interactions is not always assured, given the varied pharmacokinetic parameters associated with psychotherapeutic agents. This case report describes a patient in whom concomitant administration of nefazodone resulted in decreased clearance with resultant increase in plasma concentrations of clozapine and norclozapine.

**Case report.** Mr. A is a 40-year-old white man with a diagnosis of schizophrenia, paranoid type (DSM-IV criteria). His psychotic symptoms had been successfully treated with a combination of clozapine (425–475 mg/day) and risperidone (6 mg/day) for the last several years. An empirical trial of nefazodone was initiated to treat persistent negative symptoms of schizophrenia. Nefazodone was begun at a dose of 200 mg/day for 7 days and then increased to 300 mg/day. After a week on this higher dose, Mr. A reported increased anxiety and dizziness. Physical examination revealed mild hypotension. Therapeutic drug monitoring (TDM) documented increased plasma concentrations as well as decreased clearance of both clozapine and norclozapine (Table 1). Given the patient's signs and symp-

toms and the TDM results, the dose of nefazodone was reduced to 200 mg/day. The patient's symptoms and hypotension resolved within 1 week. At this time, a second TDM confirmed a reduction in the levels of both clozapine and norclozapine (Table 1). The clearance of clozapine and norclozapine was reduced to a greater degree when nefazodone, 300 mg/day, was coadministered compared with nefazodone, 200 mg/day.

This case report indicates that nefazodone may cause a modest, dose-dependent reduction in the clearance of both clozapine and norclozapine, with resultant increase in plasma concentration. The mechanism for this effect was not established but may be due to nefazodone inhibition of the cytochrome P450 (CYP) 3A4 isoenzyme.<sup>2,3</sup>

Nefazodone at a dose of 300 mg/day has been shown to cause substantial inhibition of the CYP3A4 enzyme and minimal effect on other major CYP450 isoenzymes.<sup>2</sup> For example triazolam, which is metabolized via CYP3A4, has shown altered pharmacokinetics when nefazodone is added. Specifically, statistically significant increases were observed in triazolam  $C_{max}$  ( $\approx 1.7$ -fold) and AUC ( $\approx 4$ -fold) 0 to 12 hours after addition of nefazodone, 400 mg/day, to a stable regimen of triazolam alone.<sup>4</sup>

The metabolism of clozapine is complex. Its major metabolite is norclozapine (desmethylclozapine). Other metabolites include clozapine N-oxide, 2-hydroxy and 7-hydroxy derivatives, and clozapine N-glucuronide. CYP1A2 is the principal enzyme mediating the formation of norclozapine.<sup>2,3</sup> N-oxide seems to be metabolized by multiple CYP enzymes: CYP3A4, 2C9/10, and 2E1.<sup>2,3</sup> Less is known about the hydroxy metabolites; however, CYP2D6 may be involved.

The *in vivo* effect of CYP3A4 inhibitors has been used to determine their relative role in the clearance of clozapine and norclozapine. For example, a formal pharmacokinetic drug interaction study examined the effect of 200 mg/day of itraconazole (a substantial CYP3A4 inhibitor) on plasma clozapine levels in 7 schizophrenic patients.<sup>5</sup> It was found that the serum concentrations of clozapine and norclozapine remained essentially unchanged. The authors concluded that CYP3A4 was of minor importance in clozapine metabolism in humans. Further, another study, conducted in 6 schizophrenic patients receiving stable doses of clozapine for at least 2 weeks, demonstrated that mean clozapine levels rose by 4% of baseline and norclozapine levels by 16% when nefazodone was coadministered at a dose of 100 mg b.i.d. for 1 week and then 200 mg b.i.d. for 2 weeks.<sup>6</sup> The authors concluded that CYP3A4 plays a minor role in the metabolism of clozapine. In each study, however, there were subjects who had reduced clearance of both clozapine and norclozapine comparable to that observed in this case report, suggesting caution when this combination of therapeutic agents is used concurrently.

In contrast, coadministration of erythromycin (another substantial CYP3A inhibitor) has been reported to significantly decrease the clearance of clozapine and norclozapine, with resultant antipsychotic drug accumulation and the development of serious adverse effects.<sup>7,8</sup> In the first case report,<sup>7</sup> the patient's clozapine level, obtained shortly after the seizure, was 1300 ng/mL at a dose of 800 mg/day for the last 3 weeks. In the second case report,<sup>8</sup> the patient's clozapine level was 1150 ng/mL at a dose of 600 mg/day for the last several months. In both the cases, there was a 33% to 54% decrease in the clearance of clozapine and norclozapine.<sup>7,8</sup> The increased drug accumulation in these 2 cases was associated with the development of serious adverse effects. One patient developed grand mal seizure followed by a period of postictal confusion. The other patient developed somnolence, disorientation, and incontinence.

**Table 1. Relationship Between Clozapine Daily Dose and 12 Hours Post-Dose Plasma Levels of Clozapine and Norclozapine as a Function of Nefazodone Coadministration<sup>a</sup>**

Drug	Daily Dose (mg/d)	Level (ng/mL)	Clearance <sup>b</sup> (dose/level)	% Decrease in Clearance <sup>c</sup>
Pre-nefazodone level				
Clozapine	450	133	3.38	NA
Norclozapine		176		NA
Total		309		NA
On high dose of nefazodone (300 mg/d)				
Clozapine	475	233	2.04	40
Norclozapine		333		44
Total		566		42
On low dose of nefazodone (200 mg/d)				
Clozapine	425	140	3.04	10
Norclozapine		230		28
Total		370		21

<sup>a</sup>Assays of clozapine and norclozapine were done by high-performance liquid chromatography. Abbreviation: NA = not applicable.

<sup>b</sup>The clearance of clozapine in the presence of nefazodone was calculated by dividing the dose of clozapine by the plasma level of clozapine.

<sup>c</sup>% change in clearance = baseline - new value/baseline.

The current case report, together with the formal studies and other documented case reports, indicates that CYP3A4 may mediate the *in vivo* clearance of clozapine and norclozapine. The relative importance varies considerably among individuals. However, caution is suggested when prescribing nefazodone concomitantly with clozapine, particularly given the dose-dependent and concentration-dependent risk of seizures associated with clozapine.<sup>6</sup> Therapeutic drug monitoring of clozapine can be used to guide dose adjustment as necessary to compensate for any reduction in clearance.

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