

## Sertraline Treatment of Hallucinogen Persisting Perception Disorder

**Sir:** Hallucinogen persisting perception disorder is the re-experiencing of the perceptual symptoms experienced while intoxicated with the hallucinogen. Examples of these perceptual distortions include geometric hallucinations, false perceptions of movement in the peripheral visual fields, flashes of color, positive afterimages, macropsia, and micropsia. Various pharmacologic treatments of "flashbacks," including neuroleptics and benzodiazepines, and electroconvulsive therapy have met with limited success.<sup>1</sup>

**Case report.** Mr. A, a 22-year-old male college student, presented to a college counseling center with symptoms of mild depression. Six months prior to his evaluation, he had stopped using lysergic acid diethylamide (LSD), after an 8-month history of LSD abuse during which he had used between 1000 to 1800 µg at least twice a week. Despite his abstinence, he noticed the persistence of LSD-like phenomena. These phenomena included visual illusions, trailing images, depersonalization, images in his peripheral field, and visions of colorful geometric forms when he closed his eyes. They occurred almost daily, were not distressing to the patient, and had preceded the onset of his depressive symptoms. He had no history of seizures or migraines.

Antidepressant treatment was begun with sertraline 25 mg and was titrated upward slowly owing to concern about these flashbacks. Mild exacerbations of these LSD-like phenomena were noted for 2 to 4 days after each dosage increase, primarily as flashes of color, positive afterimages, and fleeting hallucinations in his peripheral vision. Within 1 month after the target dose of 100 mg was reached, these perceptual disturbances decreased until they had almost completely remitted. The depressive symptoms also improved. These gains were maintained for 4 months, at which point Mr. A graduated and terminated treatment.

The pathophysiology of hallucinogen persisting perception disorder remains unclear, although several theories have been suggested.<sup>2</sup> One theory holds that LSD causes excitotoxic destruction of serotonergic inhibitory interneurons. Alternatively, these phenomena may represent visual seizures. Several measures of visual functioning indicate that patients with this disorder continue to centrally process visual imagery after the image has been removed. Despite uncertain pathophysiology, it has been observed that hallucinogen persisting perception disorder recapitulates the acute LSD experience.<sup>3</sup>

The preponderance of evidence suggests that the acute effects of LSD are serotonergic. LSD has been found to bind selectively in vivo to 5-HT<sub>2</sub> receptors and causes a drop in receptor density after one dose. Repeated administration over a 5-day period decreases binding of serotonin to the 5-HT<sub>2</sub> in the cortex.<sup>4</sup> This decrease correlates clinically with the rapidly developed tolerance to the effects of LSD. Sertraline has been shown to decrease the typical physiologic responses to serotonergic agonist on 5-HT<sub>2</sub> receptors when administered over a 2-week period.<sup>5</sup> This progressive down-regulation may account for the delayed clinical efficacy. A recent survey of LSD users who were concomitantly prescribed antidepressants found that chronic administration of serotonergic antidepressants attenuated the subjective experience of LSD.<sup>6</sup> Many of these patients

also reported LSD-like perceptual phenomena at the initiation of treatment with serotonin selective reuptake inhibitors in the absence of LSD.

It is hypothesized that hallucinogen persisting perception disorder is serotonergically mediated. Sertraline appears to have exacerbated the perceptual disturbances initially, but attenuated them after chronic administration, adding further evidence to support the serotonergic mechanism of flashbacks. The down-regulation of 5-HT<sub>2</sub> that occurs with chronic administration of a serotonin reuptake inhibitor may have provided this patient with tolerance to the remote effects of LSD.

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## Dyskinesia With Fluoxetine: Tardive or Late-Onset Persistent, Acute Norfluoxetine Dyskinesia?

**Sir:** N. H. Sandler, M.D. (February 1996 issue), reported a fascinating fluoxetine-related lingual dyskinesia.<sup>1</sup> We wish to pose some additional considerations. While these lingual movements may represent tardive dyskinesia (TD), Schooler and Kane<sup>2</sup> described properties of TD not reported in this case: masking of TD with dyskinesia drug dose increases, rebound worsening with dose reductions, and the necessity of excluding other dyskinesia etiologies.

The tardive dyskinesia properties depicted in the reported case and described in the American Psychiatric Association (APA) Task Force Report are not specific to TD. The dyskinesia case description suggests differential diagnostic considerations including fluoxetine-delayed tic provocation<sup>3</sup> in OCD (including dystonic tics), dystonia<sup>4,5</sup> (including fast dystonic movements simulating chorea), chorea, and myoclonus.<sup>4</sup> Gross thrusting lingual movements suggest dystonia. Alternative dystonia and chorea etiologies include striatal lesions associated with compulsions and dystonia<sup>6</sup> and Wilson's, Huntington's, or Sydenham's diseases. A detailed family history and laboratory investigation might prove rewarding.

The long half-life of norfluoxetine (fluoxetine's active metabolite) may delay acute dyskinesia and produce subtle onset as serum norfluoxetine levels slowly rise to steady state. It may also prolong resolution of dyskinesia without rebound worsen-

ing upon drug discontinuation as levels slowly recede. This hypothesis comports with the 5-month delay in improvement in obsessive-compulsive disorder. Hepatic disease (e.g., Wilson's disease) may further delay dyskinesia onset and offset. Norfluoxetine-inhibited presynaptic serotonin reuptake might enhance postsynaptic receptor stimulation, precipitating chorea (5-HT<sub>1C</sub><sup>7</sup> or 5-HT<sub>2</sub><sup>7</sup> receptors), dystonia (5-HT<sub>1A</sub><sup>8</sup>), or myoclonus (5-HT<sub>1A</sub> or 5-HT<sub>2</sub><sup>4</sup>). Norfluoxetine may also directly affect 5-HT<sub>2C</sub> receptors.<sup>9</sup> Thus, the movements may represent delayed acute dyskinesia rather than TD, a distinction that is important because the term *tardive dyskinesia* can imply irreversibility with substantial medicolegal liability.

Chronic fluoxetine treatment in rats reduced nigrostriatal dopamine uptake,<sup>10</sup> potentially increasing synaptic dopamine and eventuating dyskinesia analogous to levodopa dyskinesia. Notwithstanding, serotonergic inhibition of nigral neurons<sup>11</sup> might reduce basal ganglia dopaminergic tone and produce postsynaptic dopamine receptor up-regulation, a leading TD etiologic theory. Further observations may clarify these issues.

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#### Dr. Sandler Replies

**Sir:** Drs. Lauterbach and Shillcutt pose additional considerations as to the diagnosis of the patient I described as having fluoxetine-related lingual dyskinesia.<sup>1</sup> I used the diagnosis tardive dyskinesia (TD). Orobuccolingual movements occur in 80% of patients with this diagnosis. It is very common to see "fly-catcher's tongue" in TD, and this was the most marked symptom that was noted. It occurred after 3 months of treatment. The differential diagnosis of tardive dyskinesia is problematic.<sup>2</sup> The movements could very well represent acute dyskinesia rather than TD.

Drs. Lauterbach and Shillcutt encourage use of the term *dyskinesia* rather than *tardive dyskinesia* because of medicolegal liability and implications of irreversibility. Fortunately, in this case, the orofacial symptoms disappeared within 6 months after discontinuation of fluoxetine. This is compatible with descriptions of the course of the disorder where symptoms disappear in one third of the patients after discontinuation of the suspected drug.<sup>3</sup>

Drs. Lauterbach and Shillcutt did raise some interesting questions, and I appreciate their comments.

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#### Body Dysmorphic Disorder by Proxy

**Sir:** Body dysmorphic disorder (BDD), a preoccupation with imagined ugliness, has been better characterized and described in recent years.<sup>1-3</sup> Here we describe a variant (BDD by proxy) seen in two cases that involve a shift from concern over personal appearance to distress over others' appearance.

**Case 1.** Mr. A, a 39-year-old married rabbi, presented with symptoms of obsessive preoccupation with the facial and body hair of his children. He reported frequent, intrusive, anxiety-provoking thoughts lasting 3 hours/day and the need to check his children's faces, and occasionally bodies, up to 1 hour/day. These thoughts were experienced as irrational and senseless, and he reported significant guilt and despair. In addition, he spent an excessive amount of time (1 hour/day) checking his own hair in the mirror and was obsessed with how his hair "sat" on his ears. His history included significant obsessive-compulsive symptoms of doubting, checking, and symmetry concerns that were time consuming (2 hours/day), caused distress, and, at times, interfered with his functioning. For example, he had workmen dig up his backyard lawn to check whether some plumbing lines were perfectly aligned and spent the night examining them with a flashlight. As such, he met DSM-IV criteria for BDD and obsessive-compulsive disorder (OCD).

Mr. A was treated by using behavioral strategies of exposure and response prevention. Examples of in vivo exposure assignments were to look at his children to elicit the anxiety and then turn the lights down to prevent checking.

The following independent trials of medication, i.e., fluoxetine 60 mg/day, sertraline 150 mg/day, paroxetine 60 mg/day, clomipramine 150 mg/day, phenelzine 60 mg/day, and fluoxetine 60 mg/day plus pimozone 1 mg/day resulted in much improvement on the Clinical Global Impressions-Improvement (CGI) scale (1 = very much improved, 2 = much improved, 3 = minimally improved, 4 = no improvement) in the severity of both Mr. A's OCD and BDD toward himself, but did not improve BDD toward his children (CGI = 4). Behavior therapy substantially reduced his obsessive preoccupation and decreased checking of his own BDD symptoms (CGI = 2), but the

patient was dissatisfied with incomplete resolution of symptoms toward his children (CGI = 4).

**Case 2.** Ms. B, a 32-year-old attractive real estate executive, presented with anxiety about her jaw, which had been broken several years earlier. She spent a considerable amount of time (1.5 hours/day) engaged in mirror checking of her jaw and had become socially avoidant when she thought it looked ugly. Her distress and impairment of social activities were extreme at times. She had a history of OCD from childhood that included superstitious thinking, counting rituals, and obsessions of scrupulosity that resulted in hours of daily prayer. Her social and academic functioning was significantly impaired because of these time-consuming symptoms.

Soon after beginning behavioral therapy, Ms. B admitted that she had become irrationally obsessed with her fiancé's nose, which she believed to be "crooked." She became increasingly distraught, checked his nose for over 1 hour/day, and seriously considered ending the engagement. Exposure to avoided social situations and response prevention (i.e., not checking fiancé's nose and her jaw) reduced distress and allowed the marriage to take place. A follow-up phone call indicated long-term gains (CGI = 1).

These two cases suggest that BDD criteria might be expanded to include "appearance obsessions" in others. This observation highlights the need for more extensive patient interviewing given the frequency with which "typical" BDD is overlooked. The history of OCD in both cases indicates the frequent comorbidity of BDD and OCD. In addition, the children of Mr. A experienced distress about their father's daily inspections, and Ms. B's fiancé became increasingly angry over her critical attitude. These reactions indicate the potential impact of "BDD by proxy" on the other person.

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#### SSRI Optimal Dose Remains at Issue

**Sir:** Drs. Gammon<sup>1</sup> and Lane<sup>2</sup> assert that Dr. Nemeroff erred when, in his review of drug treatment of depression,<sup>3</sup> he said that most patients require more than 50 mg/day of sertraline, in distinction to other serotonin selective reuptake inhibitors, which require no more, usually, than the initial dosage: paroxetine 20 mg/day and fluoxetine 20 mg/day. They even accuse Dr. Nemeroff of bias because his paper came from a presentation supported by the makers of paroxetine. Dr. Nemeroff<sup>4</sup> defended himself by referring to dose-response literature.

I have reviewed the studies that Drs. Gammon, Lane, and Nemeroff use to support their positions, and I find I disagree with all parties, because none of the studies seems adequate to answer the question of what constitutes the optimal dose. Only

fixed-dose studies can do this. I present here a summary of such studies.

**Concerning sertraline:** Fabre et al.<sup>5</sup> randomly assigned 369 patients to placebo or one of three doses of sertraline. They found no statistically significant differences among the three doses, and all were more effective than placebo. They concluded that the 50-mg/day dose was as effective as the others (100 mg/day and 200 mg/day). But, showing that treatments do not differ significantly does not substantiate that they are the same. That requires a power analysis. They reported that 59% of subjects responded to 50 mg/day. Given their sample sizes, as I analyze their data, they had only a 20% chance of detecting a true difference of 10 percentage points of improvement, i.e., to 69% in those treated with 100 mg/day. Therefore, their finding of a 63% response rate to 100 mg/day does not prove the drugs are similar. They had a very poor chance of finding a substantial difference. The same holds true for the difference between 50 mg/day and 200 mg/day.

The other fixed-dose study of sertraline (Amin et al.<sup>6</sup>) also found no significant differences among three doses of sertraline (50, 100, and 200 mg/day), but found little difference between the active drugs and placebo. Analysis of variance of the four groups shows no significant differences on the total score of the Hamilton Rating Scale for Depression (HAM-D). Amin et al. report pair-wise analyses of the HAM-D factors, without demonstrating that the overall analysis of variance of the factors is significant, and found on one factor a significant difference between 200 mg/day and placebo (anxiety/somatization). Separate pair-wise analyses on the depressed mood factor showed that all three sertraline groups had significant superiority to placebo, but it is questionable whether we can interpret these analyses since the overall analysis of variance was not significant. On the Clinical Global Impression (CGI) scale, the combined subjects taking sertraline did not respond significantly more often than those given placebo (15/23 vs. 2/7,  $p = .2$ ; my analysis). This study, then, cannot demonstrate that 50 mg/day of sertraline has the same effect as higher doses because it does not demonstrate clearly that sertraline differed from placebo and the researchers did no power analysis.

**Concerning paroxetine:** There is one fixed-dose study (Dunner and Dunbar<sup>7</sup>) in which the subjects were randomly assigned to 10, 20, or 30 mg/day of paroxetine or placebo. The researchers found no significant differences between 10 mg/day and each of the higher doses. They did not, however, report any statistical analysis of outcome among the three doses above 10 mg/day, and I could do no further analysis based on their published data.

**Concerning fluoxetine:** Wernicke et al.<sup>8</sup> compared fixed doses of 20, 40, and 60 mg/day in 356 subjects from 10 centers. They found that on several dimensional outcome measures, fluoxetine at 20 mg/day and 40 mg/day differed significantly from placebo, but the 60-mg/day group showed a difference on only one outcome measure (Patient's Global Impression of improvement). On the categorical measure of response, all three doses showed significantly more response than placebo. Using their data, I performed a power analysis of these categorical measures. The response rate on 20 mg/day was 53% (N = 72). That gave them power of only 23% to detect a difference of at least 10 percentage points of improvement in the 71 subjects given 40 mg/day, and 9% power to detect a 5-point difference. The results are similar for the 60-mg/day group. Thus, we cannot clearly use these data to show therapeutic equivalence for these three doses.

I conclude that the data Drs. Gammon, Lane, and Nemeroff used to support their positions are inconclusive. Rather than

blame Dr. Nemeroff for his bias, we should blame all of us in the pharmaceutical industry or in academic psychiatry who have allowed this important question to go unanswered. Considering the enormous use of antidepressants, and the seriousness of the illness, it seems ludicrous that we still do not know what is the best dose for each drug.

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**Mania Associated With Serotonin Selective Reuptake Inhibitors**

**Sir:** Patients with bipolar affective disorder encounter an increased risk of mania during antidepressive therapy with tricyclic antidepressants (TCAs).<sup>1-3</sup> Serotonin selective reuptake inhibitors (SSRIs) have been demonstrated to be effective antidepressants with a low incidence of side effects.<sup>4,5</sup> While several cases of antidepressant-induced mania during therapy with the SSRIs fluvoxamine and fluoxetine have been published elsewhere,<sup>6-11</sup> we present six cases of SSRI-induced mania during antidepressive therapy with two newer SSRIs, citalopram and paroxetine.

To our knowledge, only one case of citalopram-induced mania<sup>12</sup> and no case of paroxetine-induced switch has been reported in the literature. A recent assessment<sup>11</sup> of the risks of mania associated with SSRI or TCA treatment revealed that SSRI treatment involves a significantly lower risk. Therefore, Peet<sup>11</sup> recommends SSRIs instead of TCAs in patients who are likely to develop antidepressant-induced mania. However, we think that further investigation is needed before such advice is

given, since we have observed SSRI-induced mania in 6 of 48 depression patients treated with SSRIs in the same period of time. Only 2 of these patients experienced mania while using recommended dosages of SSRI; 4 received higher dosages (60-100 mg) (Table 1). The dosages in the clinical trials of Peet were lower than those used to treat the severe depression in our patient population.

Three patients who had also been treated with lithium carbonate needed a higher dosage of SSRI, which precipitated their switch into mania. The 2 patients who experienced mania after receiving recommended dosages of SSRI (40 mg of citalopram) were both without lithium. Overall, our observations give rise to the assumption that the risk of switch into mania may be avoided by titrating SSRI dosage. It remains to be studied whether lithium prevents the SSRI-associated switch into mania in affective disorder.

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**Table 1. SSRI-Induced Mania in 6 Patients**

Case	Depression	DSM-IV	SSRI	Dosage <sup>a</sup> (mg)	SSRI Treatment Day of Switch	Days of Constant Dosage Before Switch	Lithium
1	Bipolar II	296.89	Paroxetine	60	23	(16)	Yes
2	Unipolar	296.33	Citalopram	100	56	(21)	Yes
3	Single episode	296.24	Citalopram	40	35	(27)	No
4	Unipolar	296.34	Citalopram	40	17	(15)	No
5	Unipolar	296.33	Citalopram	60	52	(40)	No
6	Bipolar II	296.89	Citalopram	100	92	(21)	Yes

<sup>a</sup>Last dosage before switch into mania. In all cases, treatment was started with 20 mg.

### Sertraline-Induced Anorgasmia Treated With Intermittent Nefazodone

**Sir:** The trend of using serotonin selective reuptake inhibitors (SSRIs) as first-line therapy for depression has brought safe, effective, and well-tolerated therapy to countless patients. However, many men and women taking these drugs (fluoxetine, fluvoxamine, paroxetine, and sertraline) experience orgasmic dysfunction. Attempts to help these unfortunate patients with cyproheptadine,<sup>1-5</sup> amantadine,<sup>6</sup> yohimbine,<sup>7</sup> and methylphenidate<sup>8</sup> have had mixed success.

Nefazodone, a new antidepressant with both serotonin reuptake pump inhibition and unique strong postsynaptic 5-HT<sub>2</sub> receptor blockade, has a less than 1% incidence of anorgasmia.<sup>9</sup> This led me to wonder if the 5-HT<sub>2</sub> receptor may be involved in the anorgasmia produced by pure SSRIs. I postulated that tonic stimulation of the 5-HT<sub>2</sub> receptor by SSRI-induced high levels of endogenous serotonin may inhibit orgasm and that blockade of this receptor might restore it.

Nefazodone has a relatively short half-life of only 2 to 4 hours and reaches peak serum levels 1 hour after oral dosing.<sup>9</sup> I reasoned that it could be given to a patient stabilized on an SSRI without causing any trouble. Further blocking of the serotonin reuptake pump would only help the patient, and blocking the 5-HT<sub>2</sub> receptor apparently does no harm. While there may be a cytochrome P450 3A4-mediated interaction between nefazodone and fluvoxamine, drug interactions should not be a problem between nefazodone and the other SSRIs.

**Case report.** Mr. A, a 31-year-old man with initially severe major depression, responded robustly to sertraline 100 mg/day. Two months into treatment, he related that he had become unable to reach orgasm, although he was aroused during intercourse. His libido had normalized, and his erectile function was normal. A trial of cyproheptadine 4 mg taken 30 minutes before intercourse had no effect on the anorgasmia.

He was maintained with sertraline and offered a trial of nefazodone taken 60 minutes before intercourse. Initially, he started with 50 mg and then increased to 75 mg. Neither dose had any effect on his continuing anorgasmia. When he increased to 100 mg, he had his first orgasm in months, but "had to work at it." Since increasing to 150 mg of nefazodone taken 60 minutes before intercourse, he has had return of normal sexual functioning. He still notes anorgasmia if he attempts orgasm within

45 minutes after the nefazodone dose. He relates that the only side effect is feeling "more energetic than usual" after taking the nefazodone. This persists until noon the day after an evening dose, but does not cause insomnia. He has not experienced sedation from the nefazodone.

This patient's experience suggests that my hypothesis about the involvement of the 5-HT<sub>2</sub> receptor in SSRI-induced anorgasmia is correct. There seems to be a dose-response curve to nefazodone's correction of this patient's anorgasmia. It is unlikely that his anorgasmia spontaneously remitted, since it continues without the use of prior nefazodone. For 6 months now, he has had no apparent ill effects from the addition of occasional doses of nefazodone to his continuing sertraline therapy.

Two additional patients I have treated have had similar benefit from the addition of intermittent nefazodone. This intervention seems worthy of further, randomized, blinded study. However, clinicians should be forewarned that some patients experience a wide range of side effects when switching from an SSRI to nefazodone. It would therefore seem likely that some patients may have problems with this combination.

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