

Drug Craving and Other Negative Reactions After Abrupt Substitution of Nefazodone for Other Serotonergic Agents

Sir: Nefazodone is a relatively new antidepressant medication with a novel profile of neurochemical effects: potent blockade of the 5-HT_{2A} receptor, inhibition of the serotonin reuptake pump at higher concentrations, and transient norepinephrine reuptake inhibition. Among the potential consequences of this profile include antidepressant and anxiolytic efficacy and decreased incidence of medication-related complaints of insomnia and anxiety. Given its reputed lack of sexual side effects, nefazodone is now regarded as a particularly useful option in cases where these side effects interfere with patient satisfaction and compliance with treatment.

We have recently observed that abrupt switches to nefazodone from serotonin reuptake inhibitors or from the serotonin and norepinephrine reuptake inhibitor venlafaxine can be associated with the emergence of anxiety, dysphoria, affective lability, agitation, restlessness, confusion, and somatic complaints such as headaches, tremors, and nausea.

We identified three cases in which these symptoms, as well as a resurgence of drug craving in abstinent patients, accompanied the introduction of nefazodone immediately after the discontinuation of fluoxetine, paroxetine, and venlafaxine respectively.

Case 1. Mr. A, a 32-year-old homosexual businessman, initially sought treatment for a major depressive episode and leg pain ascribed to HIV neuropathy. He also had a history of cocaine and opiate dependence in full remission for 4 years. The patient's depressive symptoms remitted fully on fluoxetine 20 mg/day, and his leg pain remitted with the addition of amitriptyline 50 mg at bedtime. During the year he remained on this regimen he experienced a significant reduction in sexual potency and libido, thought to be caused by fluoxetine. After the end of a sexual relationship, he elected to discontinue fluoxetine and requested an antidepressant that would be less likely to interfere with his sexual functioning. Nefazodone was prescribed at 100 mg/day on the day after fluoxetine discontinuation. During the first week of treatment, he experienced transient but severe cocaine craving and began to consume one to three cans of beer daily. He also reported increasingly severe dysphoria, marked sedation, and difficulty concentrating. In addition, he complained of feeling overwhelmed and increasingly impulsive and began driving recklessly.

Case 2. Ms. B, a 39-year-old single female professional, sought treatment for a 2-month dependence on hydrocodone bithartate 150 mg/day, which had interrupted a 10-year period of total abstinence from psychoactive substances. When initially evaluated, she was receiving paroxetine 20 mg/day for generalized anxiety disorder and dysthymia. The patient was detoxified and entered outpatient treatment, maintaining total sobriety for several months and reporting a fairly high degree of satisfaction with treatment. Her complaint of paroxetine-induced reduction of sexual interest led to a trial of nefazodone. She took 100 mg of nefazodone the night after her last dose of paroxetine and, 4 hours later, awakened in an anxious, agitated state, which was accompanied by intense opiate craving. She felt out of control and impulsively began calling physicians throughout the United States seeking prescriptions for opiates. She eventually obtained some opiates and continued to use them for 3 consecutive

days until she experienced a reduction in her agitation and dysphoria. Of note, nefazodone was discontinued after the first 100-mg dose.

Case 3. Mr. C, a 42-year-old male engineer had a history of cocaine dependence and alcohol dependence, both in remission for 6 years. During the initial evaluation, he reported a series of unsuccessful pharmacologic treatments, including various antidepressants and anxiolytics for adult-onset social phobia and panic disorder. He was subsequently started on venlafaxine 37.5 mg p.o. b.i.d., but because of complaints of delayed ejaculation, requested a trial of nefazodone. During the first day on nefazodone treatment the patient reported an unusual reaction that he likened to a "cocaine high." Subsequently, he complained of cocaine craving and an uncomfortably warm sensation on the back of his neck, but he continued nefazodone therapy in the hope that he would eventually adjust to these side effects and respond to the medication. After 1 week of treatment with nefazodone 100 mg/day, his dose was increased to 150 mg/day. Within 1 hour of this increase, he experienced dysesthesia, psychomotor agitation, impulsivity, confusion, and intense cocaine craving. All symptoms reached a peak 4 hours after ingestion of the medication and required another 7 hours to abate. Only frequent phone contacts with his therapist prevented him from leaving his workplace in search of cocaine. He had not experienced cocaine craving for more than 5 years and had never developed similar side effects on any of the numerous other psychotropic medications he had previously received.

From its neurochemical profile, nefazodone would seem to present little liability for precipitating drug craving and relapses in substance abusers who are in remission. On the contrary, many of its neurochemical affinities have been associated with enhanced prospects for maintaining abstinence. Specific serotonin reuptake inhibitors such as zimelidine¹ and specific 5-HT₂ antagonists such as ritanserin have been reported to increase alcohol intake in alcoholics. Moreover, nefazodone failed to function as a reinforcer when substituted for cocaine in rhesus monkeys.² The introduction of nefazodone seemed to abruptly precipitate cocaine or opiate relapse in two patients and unusually severe craving in another of three otherwise stably abstinent patients. The potential of this antidepressant to elicit drug craving warrants clarification.

Alternatively, although it is impossible to rule out patient factors (such as a predisposition for hypomania in our Case 1), the immediate transition from fluoxetine, paroxetine, or venlafaxine therapy to nefazodone may have precipitated substance cravings in these patients. The mechanism of this craving may be the development of a perturbation in serotonergic transmission or to altered metabolism of nefazodone, particularly if it is begun immediately after treatment with paroxetine or fluoxetine, both potent inhibitors of the P450 2D6 system. *m*-Chlorophenylpiperazine (*m*-CPP) is normally a minor metabolite of nefazodone, but with concomitant paroxetine or fluoxetine administration, *m*-CPP clearance is prolonged and levels of this compound rise significantly.^{3,4} These patients may also have been cytochrome P450 2D6 slow metabolizers, which alone or in combination with fluoxetine or paroxetine could cause *m*-CPP elevation. *m*-CPP has postsynaptic 5-HT_{2C} properties, a profile associated with the development of anxiety, dysphoria, and impulsivity in a subset of patients.⁵ Thus, this interaction between nefazodone and paroxetine or fluoxetine may precipitate symptoms that could serve as a trigger for substance

craving in vulnerable patients, particularly those who attempt to alleviate unpleasant emotional states by using psychoactive substances.^{6,7} In addition, the interaction between venlafaxine and nefazodone in the third patient might be associated with the development of a hyperadrenergic state, which could also produce symptoms capable of triggering stimulant craving in cocaine dependent individuals.

Thus, we believe that before initiating treatment with nefazodone, clinicians should consider a washout of medications that inhibit norepinephrine or serotonin reuptake, especially agents such as paroxetine and fluoxetine that also inhibit the P450 cytochrome oxidase system. It remains to be seen whether similar findings can be expected in patients with mood disorders who do not have a history of psychoactive substance abuse.

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Paroxetine-Induced Angioedema and Tongue Swelling

Sir: Serotonin selective reuptake inhibitors (SSRIs) are relatively new antidepressant medications that are rapidly gaining in popularity because they have fewer and less severe adverse effects than “older” antidepressants (e.g., amitriptyline). However, the increased use of SSRIs also allows their adverse effect profile to be more completely described. We feel clinicians should be aware of a possible association of SSRIs and angioedema.

Case report. Six hours after her first dose of paroxetine (20 mg), a 64-year-old woman developed swelling of her tongue and constriction of her throat that made swallowing difficult. In addition, the patient had diarrhea, nausea, generalized weakness, blurred vision, and mild disorientation. Information with respect to changes in blood pressure, eosinophilia, and other commonly assessed parameters was unavailable. She did not take another tablet. All of her symptoms cleared spontaneously without treatment.

The patient had been clinically depressed for the preceding 3 to 4 months and had a 41-year history of panic attacks in the setting of systemic lupus erythematosus (SLE) that involved the central nervous system. Her medical history was also significant for well-controlled paroxysmal atrial fibrillation. Her medications included prednisone (5 mg p.o. daily for the preceding 2 years as immunosuppressive therapy for SLE), warfarin, digoxin, calcium carbonate, and temazepam. She had no known drug allergies.

The timing of the development and resolution of symptoms is most consistent with an allergic reaction to paroxetine (despite concomitant prednisone), resulting in angioedematous tongue swelling. Although a reaction to an excipient of paroxetine or a drug-disease or drug-drug reaction may have been contributory, paroxetine appears the most likely cause of this patient's symptoms.

There have been rare reports of angioedema and tongue swelling associated with the use of paroxetine.¹ Even though paroxetine is structurally distinct from other SSRIs,^{2,3} similar adverse experiences have been reported with other SSRIs. Tongue edema and tongue ulceration have been associated with the use of sertraline,^{4,5} although angioedema has not been reported to date. Allergic reactions, tongue edema, and mouth ulceration have been associated with the use of fluoxetine,⁶ but angioedema has not been reported to date. There have been rare reports of tongue swelling⁷ and rare anecdotal reports of angioedema associated with the use of fluvoxamine (reference 7 and Communication from Solvay Kingswood Inc., September 26, 1994). The potential for cross-reactivity between SSRIs is not known.

Based on the above information, it is recommended that SSRIs be avoided in patients who have experienced angioedema and/or tongue swelling associated with paroxetine. Clinicians should be aware that paroxetine and other SSRIs may cause allergic reactions. The allergic reaction appears to have a unique profile of angioedema with a predilection to involve the tongue. Patients should be counseled to seek medical attention in the event of tongue swelling.

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Choosing a Dosing Strategy for Electrical Stimulation in ECT

Sir: We are writing to address some issues raised by Shapira et al.¹ (January 1996 issue). The authors report the variability and the relation of seizure threshold estimates to the efficacy of electroconvulsive therapy (ECT) with bilateral electrode placement. They state that the "initial seizure threshold for pulse bilateral ECT is highly variable and not yet amenable to accurate prediction" and recommend the stimulus titration method as it "allows threshold to be determined on an individual basis and dosage for subsequent treatments to be defined."^{1(p32)}

They based these conclusions on comparisons between different dosing techniques including our "half-age" method.² Their data, however, do not support the recommendation for the dose titration method to determine energy dosing with bilateral ECT, and they erroneously discuss the calculations of the energies defined by the half-age method. They assert that the "possibility of suprathreshold stimulation was most marked with the half-age method."^{1(p36)} In Table 4 they show that energy estimates based on "half-age" would have resulted in relationships of 0.9, 1.1, and 1.2 times their estimated seizure threshold compared with arbitrarily chosen 1.5 times of their schedule. For the age method, the energy estimates would have been 1.9, 2.3, and 2.4 times, and for the fixed dose 3.7, 3.4, and 2.8 times the estimated threshold. The highest calculated doses compared with estimated thresholds were 2.1 for half-age, 1.8 for titration, 4.6 for age, and 5.2 for fixed methods. Thus, the half-age method would assuredly not produce markedly suprathreshold stimulations, but on the contrary it would prevent overestimates. In our data,² the average dosing with the half-age method is 30% above the threshold and represents 55% of the age method, while Shapira et al. arbitrarily chose a dosing schedule at 50% above the estimated threshold.

In their discussion, they claim that with the half-age method "the variance would again have been greater than with titration and the likelihood of threshold or subthreshold stimulation increased."^{1(p37)} But their own data show a hypothesized variation of 0.4 to 2.1 for the half-age method, which is not very different than their own range of 1.2 to 1.8, despite their effort to adhere to 1.5 times the estimated threshold. The argument becomes even weaker when someone considers that, as they admit, there is a probable overestimation of threshold with their schedule.

Their complaint that the half-age method may cause the application of subthreshold stimuli is unjustified. Their calculations of thresholds are only approximate estimations since they are influenced by the titration schedule itself and by unknown effects of repeated subthreshold stimuli. In our treatment series using half-age estimates, all of our patients seized with the first stimulus during the first treatment. Such a success contrasts with the titration method, which is based on the deliberate administration of subthreshold stimuli (up to six in this study).

The argument for estimated thresholds by trial and error as they recommend, with the arbitrary dosing at 50% (or 100%) above the estimated threshold, is meant to obviate the low success rate for treatments given with unilateral placement at threshold energies, as reported by Sackeim et al.³ In the Sackeim study, no such sensitivity to threshold was reported for treatments administered through bilateral electrode placements. In bilateral ECT, we lack data arguing for a specific dosing level above threshold as more efficacious than any other estimate. The selection of energy dosing at a level of 1.5 times (which is actually 1.2 to 1.8 times) the estimated threshold is arbitrary. Until studies find a sensitivity to energy levels for treatments

with bilateral electrode placement, there is little justification for such a recommendation.

The data presented by Shapira et al.,¹ contrary to the authors' complaint, reinforce the utility of the half-age method in everyday clinical practice. If we are to consider seizure thresholds in estimating energies for seizure induction in ECT, the half-age method avoids the overstimulation that may occur with the age and fixed-dose methods and avoids the risks and the cumbersome nature of the titration method, which uses a series of unnecessary subthreshold stimuli.

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Drs. Shapira and Lerer Reply

Sir: Drs. Petrides and Fink correctly point out an error in the Results section of our paper.¹ The sentence to which they refer (in the second paragraph of their letter) should have read: "This possibility [i.e., of threshold or subthreshold stimulation] was most marked with the half-age method." This is clear from the data presented in Table 4 and is correctly stated in the Discussion section (as quoted by Drs. Petrides and Fink in the third paragraph of their letter).

The main problem with the half-age method, as identified by our findings, is not one of suprathreshold stimulation but of potentially subthreshold stimulation. This is illustrated by the range of stimulus values in Table 4. Had they been treated according to the half-age method, patients in all age groups could have received as little as 40% of the stimulus required to elicit a seizure. This problem was not encountered with the titration method. Therefore, we disagree with Drs. Petrides and Fink that a range of 1.2 to 1.8 times threshold (with titration in patients > 60 years old) is "not very different" from a range of 0.4 to 2.1 times threshold (with the half-age method in the same patients).

It is correct that the titration scale we used could have resulted in overestimation of threshold at the lowest end of the scale. Doses that would have been administered to each patient with the alternative dosing methods were compared with the threshold of that patient as defined by the titration. Therefore, for patients with thresholds lower than those actually determined in our study, the ratio of dose calculated by the half-age method to threshold could actually have been higher than we calculated. Since threshold increases with age, this problem should be less relevant in the older age group, yet the range of intensities calculated by the half-age method was as great as in the younger patients.

Contrary to the impression that is gained from Drs. Petrides and Fink's letter, we do not regard dosage titration as an ideal method for estimating seizure threshold (although it is not associated with added risk^{2,3}). Our findings suggest that it provides the closest approximation when compared with other methods.

Nevertheless, formula-based dosing is clearly preferable. Present understanding of the factors that influence seizure threshold, however, is still insufficient to provide the essential elements of such a formula. Further research on this issue is clearly indicated.

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Parotid Gland Swelling With Clozapine

Sir: Clozapine has a side effect profile that is distinct from that of the typical antipsychotic drugs. Recently, reports of unusual side effects of clozapine have included acute pancreatitis,¹ priapism,² and polyserositis.³ We report a patient who developed bilateral parotid enlargement during a trial with clozapine.

Case report. Mr. A, a 41-year-old man, was hospitalized for 14 years at a high-security hospital in England. He was given the diagnosis of paranoid schizophrenia at age 24 and was treated with multiple neuroleptics with little improvement. After 14 days of treatment with clozapine 175 mg/day, he rapidly developed painless bilateral swelling in the parotid region associated with hypersalivation. He had no fever or other systemic symptoms and no difficulty chewing or swallowing. At examination, both parotid glands were moderately enlarged, nontender, firm, and smooth. There was no lymphadenopathy, and the orifice of Stensen's duct and the submandibular and submaxillary glands appeared normal. Results of a complete blood count, SMA-7 and SMA-12, amylase, hepatic panel, thyroid function tests, and rapid plasma reagin (RPR) were all within normal limits. Serologic tests for mumps were negative for specific antibodies. Immunologic studies, including purified protein derivative (PPD), antinuclear antibodies, rheumatoid factor, erythrocyte sedimentation rate, double-stranded DNA, and angiotensin-converting enzyme levels were also within normal limits. X-rays of his jaw and chest revealed no calcifications, and EEG results were normal. Clozapine treatment was stopped. The enlargement subsided completely, with no residual signs or symptoms, within 1 week after drug discontinuation. Apart from chlorpromazine, which was prescribed on an as-needed basis, Mr. A received no other medications during the trial with clozapine.

The manufacturer of clozapine has received three reports of similar adverse reactions associated with clozapine from the United Kingdom (Pearce K. May 22, 1992. Written communication). All three reported bilateral parotid enlargement, and one case was associated with fever. In two cases, the enlargement resolved after discontinuation of clozapine, and no details are available about recovery in the third case. The clozapine dose varied from 150 to 450 mg/day. A recent report from the United States described four female patients who developed

salivary gland swelling while taking clozapine.⁴ Two of these patients had parotid gland enlargement, which resolved despite continuation of clozapine treatment.

Although we are unable to state with certainty that the parotid enlargement in our case was a direct consequence of clozapine, the temporal relationship to treatment with clozapine, absence of evidence for other etiologies, and the existence of similar cases suggest that clozapine was the cause. Parotid enlargement may be related to the peripheral adrenergic effects of clozapine in the parotid glands.⁵

Clinicians should be aware that the distinct pharmacologic properties of clozapine may result in side effects that can be very different from those of traditional antipsychotic agents and therefore either missed or attributed to other causes.

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Misuse of Naltrexone

Sir: Abuse of naltrexone when used for the treatment of opioid dependence¹⁻³ and during treatment of posttraumatic stress disorder (PTSD) has been noted.⁴ Following is a case of misuse of naltrexone when utilized solely for the treatment of alcohol dependence.

Case report. Mr. A, a 42-year-old white man with a long history of paranoid schizophrenia, currently controlled with trifluoperazine (10 mg every morning and 15 mg every night) and bupropion (2 mg p.o. every night), continued to struggle with issues related to his use of alcohol. He was enrolled in a structured day program for dual diagnosis clients. Concomitant with participation in this program, he was placed on naltrexone 50 mg/day. He had no difficulty tolerating the additional medication, but continued to use alcohol and requested an increase in naltrexone. After the dosage of naltrexone was increased to 100 mg/day, he still used alcohol but reported a decrease in quantity and frequency of drinking.

Ten months into treatment with naltrexone, Mr. A reported that he had been "abusing" the naltrexone. He stated he would take 2 to 3 tablets to obtain a calm, euphoric-type feeling. This feeling was also associated with an increase in motor energy, which he described as restlessness. Two months earlier, naltrexone had been decreased to 50 mg/day and disulfiram was added at 250 mg/day because of Mr. A's continued alcohol use. Mr. A was not known to misuse trifluoperazine or bupropion or use other illicit substances including opiates other than the occasional use of marijuana. Results of enzyme immunoassay and gas chromatography/mass spectrometry drug screens run for cocaine, opiates, and marijuana during the period of treatment with naltrexone were negative.

Lerner et al.³ report four cases of naltrexone abuse in former opiate abusers who reported a sense of well-being and euphoria associated with increased alertness and energy. The case illustrated above suggests a similar syndrome of naltrexone abuse during the course of treatment for alcohol dependence. This case is noteworthy since the patient did not have a prior history of polydrug abuse.

Possible explanations include loss of antagonist effect at higher doses of naltrexone and, in the case of someone with schizophrenia, the possibility that higher doses of naltrexone are needed for modulation of the dopamine system to treat positive symptoms,⁵ although the patient reported no exacerbation of positive symptoms.

Clinicians should be aware of the potential for abuse of naltrexone during the course of treatment for alcohol dependence, given the increasing use of naltrexone.

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Shared Obsessive-Compulsive Disorder in a Married Couple: A New Variant of Folie à Deux?

Sir: Despite the paucity of cases, dozens of papers have been written on the uncommon diagnosis of folie à deux. Perhaps one factor accounting for this interest is the rare inclusion of more than one person in a diagnosis and the fact that in all cases of folie à deux reviewed by the author, as well as in DSM-IV,¹ patients are universally defined as delusional (shared psychotic disorder), often with bizarre content in the delusions. No accounts of these patients with which the author is familiar have included obsessive-compulsive disorder or for that matter any other nonpsychotic diagnosis.

Case report. Mr. A, a 40-year-old, devoutly religious telephone worker, reported the onset of religious and contamination obsessions and compulsions in his third year of college. After struggling by himself for many months, he went to his college infirmary and was referred to a psychiatrist, who made the diagnosis of both obsessive-compulsive personality disorder and "reactive depression."

The patient was treated with tricyclic antidepressants and improved moderately only after many months of psychotherapy. Thereafter, the patient waxed and waned into a progressively insidious round of contamination compulsions. He always resisted the compulsions and recognized them as ego dystonic and useless.

This pattern continued even after his marriage in his late 20s to Mrs. A, a housewife who, although having suffered many bouts of dysthymic disorder and possessed of habitually low self-esteem, had never been treated by a psychiatrist nor reported any severe disorder of thinking or mood before her marriage.

After Mr. A had been in treatment for several years, his wife asked for an appointment and stated that she wanted to see me periodically to "help her husband." In actuality, she wanted treatment for herself. After several appointments she began to experience increased episodes of depression, with concomitant anxiety. Upon repeated questioning, Mrs. A denied any obsessive-compulsive symptomatology before her marriage, and any history that would alert one to a psychosis.

Mrs. A gradually revealed a "hidden" (by her description) symptom pattern consisting of numerous obsessions and more numerous compulsions. She maintained that the severity of the compulsions rose and fell in concordance with not only her own life stressors but also the degree to which her husband acted out his contamination compulsions.

The content of her compulsive rituals was identical to her husband's. While she would add her own unique variants to these contents, the parameters remained limited, and she at no time reported any thought or major mood disorder.

Mr. and Mrs. A satisfied exactly the criteria for shared psychotic disorder, or folie à deux, in DSM-IV¹ except for the fact that the patients happened not to be psychotic. This by no means points to a conclusion, however, that Mr. and Mrs. A could not be diagnosed as folie à deux.

If one substituted the word *contamination* for *induced psychotic disorder*, then all other variables traditionally listed under the rubric of folie à deux would apply to this couple.

What the case does illustrate is the overly confining nature of the defining aspects of folie à deux in modern psychiatric nosology. Similar points have been made by Sacks² and Lazarus³ and perhaps most strongly by Munro,⁴ who states that "in truth, the majority of individuals with folie à deux are not psychotic: they tend to be impressionable people who adopt untrue beliefs as a result of a long and over-close association with a deluded person."

This case would seem to bear out Munro's observation, and at the very least offers the opportunity for the inclusion of folie à deux in the border areas of conventional thinking about neurosis and psychosis. Thus the question arises again: where obsessions and compulsions develop in the context of an intense relationship and this content is almost identical in substance and timing in a secondary partner who was previously free from disorder, are we dealing with folie à deux or is obsessive-compulsive disorder more delusional at times than previously supposed?

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