

Reversible Dyskinesia During Bupropion Therapy

Sir: Rare instances of choreoathetoid dyskinesias have been observed with tricyclic antidepressants, trazodone, amoxapine,¹ and serotonin reuptake inhibitors,² but unlike neuroleptic-induced tardive dyskinesias, those associated with antidepressants tend to remit after drug discontinuation. Reversible dyskinesia may also occur with the atypical antidepressant bupropion, as the following case illustrates.

Case report. A 70-year-old married woman had been treated with lithium carbonate for bipolar disorder for over 20 years. At 300 mg b.i.d., her serum lithium levels were in a narrow therapeutic range of 0.6 to 0.8 mEq/L, and she was clinically stable until the current episode. She was concurrently receiving nicardipine 20 mg/day for hypertension and levothyroxine 0.05 mg/day for lithium carbonate-induced hypothyroidism. She was stable medically, and there was no substance abuse history.

In mid-1995 she presented with depressed mood, lack of interest, low energy, decreased appetite, and feelings of impending doom. There were no obvious precipitants for this depressive episode. Sertraline was added to lithium carbonate and was raised gradually from 25 mg to 100 mg daily. The patient's mood improved slightly, but she remained anergic. Sertraline was therefore tapered and discontinued over 1 week, and bupropion 75 mg/day was started. After only 2 days on bupropion treatment, she experienced abnormal eye movements and on examination showed frequent eye blinking and blepharospasm of both eyes. The bupropion dose was raised in two increments to 225 mg/day, and after a total of 6 weeks on this bupropion dosage, her depressive symptoms remitted completely. However, the patient's dyskinesia progressed, and her tongue became affected. After 3 weeks on bupropion 225 mg/day, she exhibited frequent eye blinking, moderately severe blepharospasm, curling tongue movements, as well as other side effects of hand tremor, nausea, and dizziness. Since the serum lithium level stayed at 0.6 mEq/L, the side effects were assumed to be caused by bupropion, and its dose was reduced to 150 mg/day. The dyskinesia began to recede, and all other side effects disappeared. During the next 4 months, bupropion was gradually tapered and eventually discontinued. Six months after bupropion withdrawal, the patient remained in clinical remission on lithium carbonate 300 mg b.i.d. (latest serum level = 0.6 mEq/L) and was showing only occasional curling of her tongue. The eye symptoms also remitted.

Our patient, who had no previous exposure to neuroleptics, developed a reversible orofacial dyskinesia affecting the eyes and tongue while receiving bupropion 75 to 225 mg/day for bipolar depression. The observed blepharospasm suggests dystonia. However, it did not indicate oculogyric crisis because of the absence of the rolling up of the eyeball and the lack of marked distress. The blepharospasm was not accompanied by the oromandibular dystonia typical of Meige syndrome. The presence of frequent eye blinking, blepharospasm, and curling tongue movements is best regarded as an orofacial dyskinesia with choreoathetoid and dystonic components.

The sequence of events seems to implicate bupropion as the cause of the orofacial dyskinesia. Sertraline was discontinued within days of the onset of the first signs of dyskinesia. A prolonged withdrawal dyskinesia from sertraline has not been reported and seems very unlikely. Lithium carbonate was prescribed for many years without extrapyramidal symptoms,

and the serum lithium levels were at low therapeutic levels throughout the period of dyskinesia. While lithium carbonate is therefore highly unlikely to have induced the dyskinesia, the role of lithium as a possible contributing factor cannot be excluded. Ghadirian et al.³ suggested that lithium may exacerbate the vulnerability of affective disorder patients to dyskinesia. As the dose of bupropion was reduced and eventually discontinued, the severity of the abnormal movements simultaneously improved, and eventually the dyskinesia resolved.

I have personally observed two other patients concurrently treated with neuroleptics where bupropion aggravated tardive dyskinesia. In all three cases, the additional observed symptoms were indistinguishable from tardive dyskinesia. The mechanism of action whereby bupropion induces dyskinesia may involve dopamine reuptake inhibition and the enhancement of norepinephrine functional activity.⁴ One may speculate that once bupropion is withdrawn, the excess catecholamine activity may also dissipate, and the dyskinesia may subsequently remit. As was observed in the patient described here, the risk/benefit equation may favor the continuation of bupropion therapy even in the presence of orofacial dyskinesia, at least for a limited time period if the antidepressant response is clearly favorable. As with other drug-induced reversible dyskinesias, the condition is expected to resolve after drug discontinuation.

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A Case of Seasonal Trichotillomania

Sir: We report the case of a patient who had both winter seasonal affective disorder (SAD)¹ and trichotillomania with winter exacerbation, whom we treated with light therapy.

Case report: Ms. A, a 24-year-old woman, had a history of trichotillomania since 10 years of age. From the onset of symptoms, the trichotillomania persisted across the year, but improved in the summer, when she needed no special head covering, and worsened in winter, when she would habitually develop a bald spot 5 cm in diameter. For the past 6 years, she experienced fall and winter depressive episodes characterized by sadness, lethargy, anhedonia, hypersomnia, increased appetite and weight, decreased socialization, and increased hair pulling. Although she never experienced a full remission of trichotillomania, the winter exacerbation and summer amelioration of symptoms had become more prominent over the past 6 years. According to the patient, neither depressive symptoms nor trichotillomania responded to treatment trials with fluoxetine in December 1991 and sertraline in October 1992.

We treated the patient with light therapy (10,000 lux, 1 hour twice a day) for 6 weeks during the winter, when she was mildly

depressed and suffering from marked trichotillomania. She was taking no antidepressant medications during this time. Although she reported a moderate improvement in mood and energy level, there was no evidence of reduced severity of trichotillomania, as rated by three standard measures.²

The evidence that brain serotonergic systems are dysregulated in both obsessive-compulsive disorder and seasonal affective disorder^{3,4} suggests that light treatment may be of benefit in patients with obsessive-compulsive disorder. Our results are consistent with reports of winter exacerbation of obsessive-compulsive disorder symptoms⁵ that have been shown to be less responsive to the type of light therapy that has been effective for SAD.

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Clozapine-Related Speech Disturbance

Sir: Dr. Bak and colleagues¹ (September 1995 issue) reported a case series of clozapine-dose-related myoclonus and noted that at least several were intensified by psychological stress. As this particular side effect is receiving greater attention, yet its incidence is still vague, I report here the dose-related occurrence of orolaryngeal myoclonus in a patient treated with clozapine.

Case report. Mr. A, a 40-year-old man with chronic schizophrenia, was hospitalized for exacerbation of psychotic symptoms, agitation, and paranoid delusions. The patient had no history of seizure disorder. He had been previously treated with several traditional neuroleptics without benefit.

He was begun on clozapine and titrated up to 400 mg/day. He was concurrently begun on sertraline 50 mg/day for depression. After 1 month, Mr. A's paranoia, delusions, and irritability were significantly decreased, and his mood became euthymic. However, it was at this time that he developed a new-onset speech disturbance, best described as a grunting or "hiccupping" motor tic. The disturbance occurred only during speech and was intensified by psychological stress. Mr. A reported that "my throat and mouth get tight." No facial or extremity myoclonus was visible; no changes in mentation were observed. No obsessive-compulsive symptoms were reported. Mr. A was observed closely over a week, but he had no resolution of his vo-

cal myoclonus. His distress increased because the motor tic prevented him from completing sentences.

The reduction of the clozapine dose to 350 mg/day was accompanied by an immediate reduction in the intensity of his speech disturbance. A clozapine level obtained at this time was 870 ng/mL. As his dysarthria persisted, this was considered only a partial remission of symptoms, and his clozapine was lowered to 250 mg/day over the next week. At this point, Mr. A's speech disturbance had completely abated, and a follow-up clozapine level was 480 ng/mL. He remained psychiatrically stable and evidenced no further myoclonus.

Clozapine has been previously reported to cause a dose-related increase in major motor seizures as well as myoclonus²; however, the exact incidence of myoclonus during clozapine treatment remains uncertain. This case lends further support to the findings of Bak et al., who reported five cases of apparent dose-related myoclonus, one of which bore striking similarities to our patient with regard to speech disturbance and worsening with psychological stress. It is possible that sertraline may have directly induced myoclonus, or indirectly by increasing clozapine levels. However, my patient's symptoms were time-linked with dose changes of clozapine, as seen by the apparent relief associated with dose reduction.

It is of interest that serotonin agonists have been implicated in both the induction and treatment of myoclonus.^{3,4} Since myoclonus has not been reported with traditional neuroleptics,⁵ there is the possibility that clozapine's serotonergic activity may be responsible. The picture becomes confounded with the addition of SSRIs, and it may be that a complex balance of serotonergic neurotransmission is involved.

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Drs. Bauer and Reischies Reply

Sir: We are pleased at Dr. Knoll's interest in our report¹ on clozapine-induced myoclonus. Similar to the course in four of our patients, clozapine-related myoclonus in the case described by Dr. Knoll was relieved after clozapine dose reduction. We have gathered more positive experience with the addition of carbamazepine in clozapine-induced myoclonus, a procedure we apply if a clozapine dose reduction is connected to a significant deterioration in psychotic symptoms in otherwise neuroleptic-resistant schizophrenics. Interestingly, our results are confirmed in a recent report by Sajatovic and Meltzer.² They

reported clozapine-induced myoclonus and generalized seizures in 11 (7.4%) of 148 patients with schizophrenia or schizoaffective disorder who were treated with clozapine mono-therapy; in four patients the addition of phenytoin led to the resolution of myoclonic activity. There is now increasing evidence from basic and clinical research that serotonin plays a key role in myoclonus.³ This hypothesis is being confirmed by recent reports on myoclonus induced by antidepressants acting via serotonin selective reuptake inhibition.⁴⁻⁷

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Paroxetine-Induced Anorexia in a Patient With Bulimia Nervosa

Sir: Drs. Vaz and Salcedo¹ recommended reducing dosage and continuing treatment of bulimia with the same serotonin selective reuptake inhibitor (SSRI) if anorexia occurs as a side effect. Recently, several SSRIs have demonstrated utility in treating bulimia nervosa and depression.²⁻⁶ I report the induction of anorexia (and possibly hallucinations) in a patient diagnosed with bulimia nervosa and depression who was taking an SSRI. I suggest considering switching a patient's medication to a different SSRI (at an equivalent dose) if anorexia is induced by the first SSRI.

Case report. Ms. A, a 27-year-old woman, was admitted with a DSM-IV Axis I diagnosis of adjustment disorder with depressed mood. At admission she weighed 62.3 kg (137 lb), at a height of 161.3 cm (5'3½"). She was complaining of suicidal thoughts induced by several stressors including an impending court hearing for the custody of her children. Ms. A had been hospitalized after five suicide attempts. Her childhood history included sexual abuse by male relatives (beginning at age 5 and continuing until age 15 years).

At admission, Ms. A reported that she had been refusing to maintain her body weight and was preoccupied with thoughts of "being fat and getting fatter," although she seemed to have a normal weight. Her anxiety about "being too fat" had led her to avoid food or liquids several times in the past. She also admitted to recurrent episodes of binge eating, feeling lack of control over her eating behavior during these binges, and engaging in self-induced vomiting using laxatives, strict dieting, and vigorous exercise. She was overly concerned with body shape and weight.

On the second day of her admission, Ms. A was started on paroxetine 20 mg in the morning. Two days later, she reported feeling a little better. The next day she complained of intermittent nausea and vomiting; however, she refused taking the medicine that was offered to stop these symptoms. No physical cause was found. Two days later, Day 7, she felt a little better and started eating "a few bites." Later that same day, for the first time, she reported auditory hallucinations which were telling her that she was bad. Therefore, thioridazine 50 mg at nighttime was added to the regimen. She also agreed to start cyproheptadine hydrochloride 2 mg in liquid form 1 hour before each meal three times a day. On Day 10, 3 days later, Ms. A was free of suicidal thoughts.

On Day 11, which was 9 days after paroxetine was started, recording of her fluid intake and output began. She was encouraged to increase her fluid intake after she suffered mild dehydration. Her weight was 60.6 kg (133¼ lb). Two days later, she reported feeling "too fat," was refusing meals, was weak, and stumbled at times. Supplemental canned liquid food was offered three times a day with meals, and a dietary consultation was requested. On interview, she reported feeling more energetic, but increasingly less hungry and more fat. She agreed to switch to sertraline at a bedtime dose of 50 mg.

Four days later, Day 17, she still reported feeling down and guilty about her weight and agreed to increase her sertraline dose to 100 mg at nighttime. The dietary consultation revealed that her weight remained at 60.6 kg (133¼ lb) (ideal body weight = 53.4 kg [117½ lb] ± 10%). Also, her body mass index was 23 (normal range, 19-25). These findings helped us to rule out a diagnosis of anorexia nervosa.

On Day 23 of her stay, the patient was discharged in fairly good condition, eating, sleeping, and feeling strong enough to take care of herself and her children. She was discharged on a regimen of sertraline and thioridazine.

The induction of anorexia (not anorexia nervosa) by paroxetine in this case seems very likely. If the anorexia were induced by cyproheptadine, it probably would have continued after paroxetine was withdrawn. Weight gain secondary to increased appetite is a more frequently reported side effect of cyproheptadine. The hallucinations may have been induced by paroxetine, since the onset was within five half-lives (steady-state). They also could be part of the depressive symptomatology. The improvement of appetite in anorexia, due to antidepressant effect,⁷ could be caused by cyproheptadine, thioridazine (weight gain being a common side effect), or the combination of the three drugs. In their letter, Dr. Vaz and Dr. Salcedo recommended reducing the dose and continuing the same SSRI if and when anorexia occurred.¹ However, considering the risks versus benefits and the availability of different SSRIs, trying a comparable dose of a different SSRI sounds reasonable. This strategy seemed to work with my patient. It should be noted that my patient was also receiving intensive supportive therapy, cognitive therapy, group therapy including a grief and loss group, and support from one family member and visits by her children. These psychological factors have also been factors in patients' improvement. Although these interventions started early after her admission, they seemed to work better after the SSRI "switch." It is my suggestion to switch to a comparable dose of SSRI rather than decreasing the dose in similar cases, since lowering the dose can lead to the recurrence of depressive symptoms. If the "switch technique" fails to eliminate the anorexia, the next step would be reducing the dose and continuing all other therapeutic interventions.

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Dr. Vaz Replies

Sir: Dr. Sagduyu refers to a letter published by Dr. Salcedo and me in 1994 reporting the intermittent and dose-dependent appearance of anorexia in a bulimic patient (with antecedents of anorexia nervosa) treated with fluoxetine. Dr. Sagduyu reports the case of a bulimic patient who presented severe adverse reactions (including anorexia) after the administration of paroxetine 20 mg/day, and a fair response to sertraline. He concludes that when anorexia occurs as a side effect after the administration of an SSRI antidepressant, the best procedure is to switch to a different SSRI rather than maintaining the first drug with a lower dosage.

I would like to highlight three important points. The first regards our letter. When we published it, our intention was not to discuss treatment-related issues, but to raise the necessity to establish “biochemical subtypes” within the bulimic spectrum, and to relate them with clinical subtypes and with drug response. The usefulness of identifying clinical subtypes of bulimia nervosa has been widely defended in recent years, and in fact some clinical subtypes of anorexia nervosa and bulimia nervosa have been included in the DSM-IV. Our suggestion was that “biochemical subtypes” may fit with some “clinical subtypes,” and that the first dimension may be able to determine the appearance of some specific complications when drugs with strong effect on eating behavior (i.e., fluoxetine) are used.

The second point regards the case of Ms. A. Dr. Sagduyu describes a bulimic patient who presented gastrointestinal symptoms and auditory hallucinations after the administration of paroxetine. Anorexia occurred in this patient as well as other gastrointestinal symptoms (i.e., nausea and vomiting), which is a frequent complication when paroxetine and other SSRIs are used. Ms. A was a depressed woman with a severe adjustment disorder. We have no data on the existence of personality features, but perhaps borderline and/or histrionic traits may exist (explaining the recurrent suicidal behavior and the high mood reactivity).¹ Perhaps a diagnosis of “multi-impulsive” bulimia could be applied to this patient.² In this context, a DSM-IV sub-

stance-induced psychotic disorder with hallucinations (293.82), due to antidepressants (E939.0), seems to be supported, leading to the discontinuation of paroxetine and the concurrent administration of thioridazine. Idiosyncratic factors and the medical status of the patient (dehydration and other possible metabolic disturbances) could be implied in the appearance of the aforementioned disorder. On the other hand, and from a psychodynamic point of view, the content of the hallucinations seems to be related to the underlying eating problems. In anorexic and bulimic patients, the control over the body is strongly related to the feeling of control over the self. The idea of being “bad” (unable to control the self) is not too far from the idea of being “fat” (unable to control the body). Some bulimic patients could experience the appearance of drug-induced vomiting and other bulimic symptoms as a loss of control over the body functions, and strong feelings of fear, depreciation, and guilt could arise. Therefore, the appearance of eating-related side effects could have a special meaning for eating-disordered patients, inducing the strong reactions. Anyway, the case described by Dr. Sagduyu seems to be very different from the case that Dr. Salcedo and I described. The drug-induced anorexia, which in our patient was a very selective and dose-related symptom, seems to be a secondary phenomenon, emerging among a constellation of side effects, in the case described by Dr. Sagduyu.

The last comment relates to the general way of treating bulimic patients with antidepressants and other psychotropic drugs. Bulimia nervosa is a complex condition, which integrates psychological, psychiatric, and medical features. The pharmacologic treatment of bulimic patients is often very difficult, because the existence of added factors, such as suicide risk, use of other drugs and/or alcohol, and a belief system opposed to medication, can be serious obstacles.³ The appearance of side effects can complicate the process, especially if they interfere with the way the patient maintains his/her self-esteem and his/her feelings of mastery and control. So, as clinicians, we must avoid rigid ideas about how to manage our cases. The medical status of the patient can make the use of low initial doses of medication advisable in some cases. In other cases, the lack of a clear response or the appearance of severe side effects might lead us to look for the better tolerated drugs. In most cases, psychotherapeutic and pharmacologic procedures are complementary and partially responsible for the improvement of the patient, with the report by Dr. Sagduyu serving as a good example of this last assertion. Thus, a psychoeducational program centered on the nature, effects, and management of medication might be needed in some cases before starting drug treatment in order to increase the patient’s tolerance to side effects, to assure compliance, and to reduce physical and psychological complications.

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