

## Clinical Manifestations of Dystonia and Dyskinesia After SSRI Administration

**Sir:** Dr. Leo's recent article<sup>1</sup> suggests a definite association between SSRIs and movement disorders. Ascertaining causality from case reports is difficult, especially when recent or concurrent use of psychotropic medications is not well documented. Moreover, akathisia is difficult to differentiate from anxiety in most reports. Nevertheless, we reviewed data covered by Dr. Leo's literature review, focusing on more clear-cut instances of dystonic and dyskinesic reactions in which SSRIs loom as the primary offending agent. We undertook a MEDLINE search employing the terms *dyskinesia*, *tardive dyskinesia*, and *dystonia* in relation to the commercially available SSRIs. We limited our review to dyskinesia, chorea, and dystonia where SSRIs were likely the sole dyskinesic agent. Several cases illustrating some clinical features of these movement disorders are discussed below.

### Case Discussions

Reccoppa et al.<sup>2</sup> reported on a 22-year-old woman with major depression who achieved a partial response during treatment with fluoxetine 20 mg/day for 3 months. Ten days after the dosage was increased to 40 mg b.i.d., the patient presented to the emergency room with anxiety, severe trismus, and stiffness of tongue and neck. She had had no exposure to neuroleptics or antidopaminergic agents, but she took thyroxine 0.075 mg/day. Results of a routine laboratory workup were unremarkable. The dystonia remitted after diphenhydramine 50 mg, and this dose was repeated 5 hours later. Fluoxetine and thyroxine were discontinued, and thyroxine was restarted uneventfully shortly thereafter. Three weeks later, fluoxetine 20 mg/day was readministered, and trismus and tongue and neck stiffness developed 7 days later. Trihexyphenidyl 5 mg produced substantial improvement, and treatment was continued at 5 mg b.i.d. for 3 days.

Shihabuddin and Rapport<sup>3</sup> discussed a 35-year-old man with first-onset major depression. Sertraline dosage was started at 50 mg/day and was titrated over 2 weeks to 200 mg/day. After 3 days at 200 mg/day, he complained of bilateral jaw stiffness, left-sided torticollis, and probable akathisia. Diphenhydramine 50 mg orally every 4 hours for 5 days produced complete resolution. Due to subarachnoid hemorrhage 8 years earlier, CT and SPECT imaging was obtained, revealing no acute findings.

Al-Adwani<sup>4</sup> reported a 32-year-old man with a depressive disorder and left hemiparesis status post pontine hemorrhage at age 21. Left-sided dystonia resulting in inability to ambulate developed several days after the start of treatment with paroxetine 20 mg/day. Dystonia resolved 1 week after paroxetine was withdrawn.

Sandler<sup>5</sup> reported a 29-year-old man with childhood-onset compulsions. He improved on fluoxetine titrated to 80 mg/day over 5 months. By 12 months, however, he developed dyskinesia of the extremities, face, and mouth, with "gross" tongue thrusting resembling tardive dyskinesia. The dyskinesias diminished 2 months after fluoxetine cessation. Mouth movements resolved 4 months later.

### Conclusion

Any review of the literature is subject to the inherent limitations of the published data, potential confounding etiologies,

and ambiguous descriptions of movement disorders. Reports documenting rechallenge of a patient with the supposed etiologic agent are rare; moreover, the paucity of reported cases in which an SSRI was the sole drug involved also hampers broad conclusions. Nevertheless, SSRI-induced movement disorders appear to be a real, albeit uncommon, phenomenon to which the clinician should be attuned.

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### Dr. Leo Replies

**Sir:** I recently reviewed 71 cases of new-onset extrapyramidal symptoms (EPS), including akathisia, associated with SSRI use.<sup>1</sup> Nearly 58% of affected patients were administered medications in addition to the SSRI. In several of these, the coadministered drug was capable of producing EPS. The temporal relationship between onset of EPS and SSRI initiation, or dose increase, or resolution of EPS with SSRI discontinuation implicated the SSRI in these movement disorders. Reports indicating rechallenges with the SSRI were indeed rare.<sup>2,3</sup> Therefore, in reviewing cases of SSRI-associated EPS, I acknowledged the potential confound of concomitant drug administration.<sup>1</sup>

On the other hand, it is not uncommon for patients to be prescribed more than one medication simultaneously. In those cases in which an SSRI was coadministered with an agent capable of producing EPS, pharmacokinetic interactions may have occurred, leading to increased availability of the SSRI, the concurrently administered drug, or both. These, in turn, may be responsible for the movement disorders observed. For example, serum levels of haloperidol<sup>4</sup> and pimozide<sup>5</sup> reportedly increased with fluoxetine coadministration, which might increase the likelihood of EPS. Additionally, medications that do not produce EPS may, when combined with an SSRI, predispose the patient to movement disturbances. One patient who had been prescribed fluoxetine uneventfully for 1 year developed parkinsonism after the addition of cimetidine.<sup>6</sup>

As of December 31, 1996, postmarketing surveillances indicated 383 cases of dystonia, 403 cases of akathisia, 503 cases of parkinsonism, and 120 cases of tardive dyskinesia associated with the use of fluoxetine, sertraline, and paroxetine (data on file, Lilly Research Laboratories, Indianapolis, Ind.; Pfizer Labs, New York, N.Y.; SmithKline Beecham Pharmaceuticals, Philadelphia, Pa.). Given that patient marketing of the afore-

mentioned SSRIs is estimated to exceed 30 million, movement disorders associated with SSRI use are uncommon.

Any review of case reports or postmarketing surveillances is limited by potential confounds, e.g., recent drug use or drug coadministration. Clinicians may not always be apprised of recently administered or coadministered medications; thus, the possibility of drug interactions resulting in EPS must be entertained. Further experience and large scale prospective studies are required to confirm the causal relationship between SSRI use and EPS.

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#### Oxybutynin and Intranasal Desmopressin for Clozapine-Induced Urinary Incontinence

**Sir:** In their report on the efficacy of ephedrine in the treatment of clozapine-induced urinary incontinence, Fuller et al.<sup>1</sup> report that in their clinical experience with hospitalized psychiatric patients oxybutynin was ineffective in the management of this side effect. We have found both oxybutynin and intranasal desmopressin to be effective in the treatment of outpatients with clozapine-induced urinary incontinence.

As part of the Continuing Care Division, a community-based program of services for the severely and persistently mentally ill, the Clozapine Treatment Program provides case management and medical services to 71 patients with treatment-resistant psychosis managed with clozapine. On the basis of patient or family self-report, we identified seven cases of clozapine-induced urinary incontinence. Six cases arose de novo after the initiation of clozapine, and one case represented exacerbation of preexisting stress urinary incontinence. Five of the patients were women and two were men; they ranged in age from 26 to 43 years. The dose of clozapine ranged from 300 to 900 mg/day. One man was treated with lithium in addition to clozapine. Lithium can cause polyuria, which may exacerbate the clozapine-induced urinary incontinence.

Five of the seven patients were treated with oxybutynin, in doses ranging from 5 mg at bedtime to 5 mg three times a day. The two other patients were treated with intranasal desmopressin. Because of the risk of hyponatremia, these two patients were carefully screened to rule out psychogenic polydipsia as a contributor to the incontinence and thus a potential complicating factor in the use of desmopressin. All seven of these patients had resolution of their incontinence with treatment.

The incidence of urinary incontinence in our population was much lower than that found by Fuller et al.<sup>1</sup> However, we identified urinary incontinence only by subjective complaints, an ap-

proach that underestimates the actual incidence. In at least one case, a patient's mother repeatedly noted that he was incontinent at night, but he continued to deny any problems with bladder control.

In our population, oxybutynin was effective in the control of clozapine-induced urinary incontinence. The difference between our experience and that of Fuller et al.<sup>1</sup> may be related to differences in the populations involved: inpatient versus outpatient status, severity of illness, etc. In their series of nine patients with clozapine-induced urinary incontinence, Frankenburg et al.<sup>2</sup> found both oxybutynin and intranasal desmopressin to be effective. Interestingly, they were able to treat one patient by alarm clock arousal as a prompt to empty the bladder during the night. We think that it is premature to discount the role of oxybutynin for the treatment of clozapine-induced urinary incontinence. Our patients are well served by the availability of multiple treatments.

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#### Dr. Fuller and Colleagues Reply

**Sir:** We are pleased that others have confirmed our observation of urinary incontinence associated with clozapine. We agree that, absent systematic ascertainment, the actual incidence of this troublesome side effect is likely to be underestimated. Lurie and Hosmer report that they have had success in treating this side effect with oxybutynin. In our hands, this proved to be ineffective. However, as we reported, the likelihood of urinary incontinence was increased in those patients treated with a combination of both clozapine and a typical antipsychotic medication. We did not try oxybutynin in patients with urinary incontinence treated only with clozapine. Perhaps this accounts for the differences in efficacy we observed and that which Lurie and Hosmer observed. Although we tried intranasal desmopressin, we felt that the risks and expense inherent in the use of this drug outweighed its benefits. We agree that patients treated with clozapine are well served by the availability of multiple treatments for side effects.

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#### Oxcarbazepine for Panic Disorder Occurring After Two Grand Mal Seizures: A Case Report

**Sir:** Recently, pathophysiologic relations between panic disorder and epilepsy, at least in a subgroup of patients, have been hypothesized,<sup>1,2</sup> and thus the rational use of anticonvulsants in

panic disorder has been proposed. Several preliminary non-placebo-controlled studies<sup>1,3</sup> used carbamazepine successfully in panic disorder, even though one non-placebo-controlled study found carbamazepine ineffective.<sup>4</sup> Oxcarbazepine (Trileptal) is a new anticonvulsant substance with a chemical structure related to that of carbamazepine but with quite different metabolic pathways and active metabolites.<sup>5</sup> Oxcarbazepine has not been studied in panic disorder yet. We present a patient who developed panic disorder after suffering from two grand mal seizures and in whom both conditions were relieved by oxcarbazepine.

**Case report.** A white man was healthy until the age of 23 years when he experienced an isolated grand mal seizure. The seizure occurred after the consumption of three glasses of wine. The patient had no prior history of alcohol or substance abuse or dependence. He was then symptom-free for 6 months without treatment until a second grand mal seizure occurred, again after the consumption of alcohol. Subsequent inpatient examinations revealed normal somatic, psychiatric, and clinical neurologic status. EEG showed right high temporal sharp waves without signs of increased excitability. A diagnosis of alcohol-related seizure was made. Treatment was started with oxcarbazepine at 600 mg/day.

Two weeks later, typical panic attacks occurred. The attacks had peak-onset within 3 minutes and lasted for about 15 minutes; on average, they occurred twice a day for 4 weeks until the patient was referred to our department. Symptoms included fear of dying, palpitations, tremor, derealization, sweating, and restlessness. No alterations of consciousness or convulsions were associated with the panic attacks. The patient developed anticipatory anxiety but no agoraphobia. Examinations again revealed a normal somatic and neurologic status. The patient had stopped drinking alcohol completely after his second seizure.

The patient was interviewed with the Structured Clinical Interview for DSM-III-R (SCID) by two psychiatrists, and a diagnosis of panic disorder without agoraphobia was made. No other diagnosis was found. Results of EEG and magnetic resonance imaging of the whole brain were normal.

Since we have had good experience so far with anticonvulsants in the treatment of atypical panic disorder,<sup>1</sup> we increased oxcarbazepine to 900 mg/day. Two weeks later, the patient was symptom-free, had no side effects from oxcarbazepine, especially no sedation, and remained in this state at a 6-month follow-up.

We suggest that our patient had a primarily lowered seizure threshold, which led to both the alcohol-related seizures and the panic disorder. This lowered threshold seems to be the most likely cause for the isolated seizures, because a single dose of alcohol may increase seizure susceptibility.<sup>6</sup> On the other hand, it is important to point out that seizures often serve as a nonspecific stressor for the onset of psychiatric symptomatology.

The therapy response of both conditions, panic disorder and seizures, to oxcarbazepine suggests a pathophysiologic relation between the two. We suggest that this case adds evidence to the hypothesis that anticonvulsants might be an appropriate treatment in patients with atypical panic disorder even though the possibility cannot be ruled out that clinical improvement in this patient could be related to placebo-effects or the natural history of the illness.

Since oxcarbazepine has been shown to have a safe side effect and interaction profile while showing comparable efficacy with other anticonvulsants,<sup>5</sup> it might be a promising substance for further research in panic disorder. Clearly, placebo-controlled trials with oxcarbazepine in panic disorder patients without EEG findings and no history of seizures are needed.

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### A Novel Placebo Lead-In Behavior Strategy for Sertraline Dosing in a Depressed Patient Highly Sensitive to Medication Side Effects

**Sir:** Medication compliance in mood disorders is a complex process that challenges patients and clinicians.<sup>1</sup>

**Case report.** I report the successful treatment of a 49-year-old woman with a 20-year history of major depressive disorder, recurrent type without full interepisode recovery, who had previously discontinued several trials of antidepressant medications due to side effects. Earlier treatments with psychoanalysis, group psychotherapy, and individual supportive psychotherapy failed to relieve symptoms of depression. Antidepressant trials had previously begun with the lowest commercially available dosage of representatives from several classes including TCAs, MAOIs, and SSRIs. Typical side effects included headache, fatigue, blurred vision, and constipation. Augmentation strategies with lithium and thyroid hormone were also unsuccessful.

The patient acknowledged strong apprehensive feelings about further trials of antidepressant medication and believed that earlier experiences would lead her to anticipate side effects. In an effort to minimize the effects of anticipation, the patient agreed to a double-blind lead-in titration schedule in which identical unmarked capsules were administered daily through a dosette preloaded by the hospital pharmacy. The patient was informed that treatment would begin with a placebo lead-in followed by an escalating dosage schedule starting with sertraline 12.5 mg followed by dosage increases of 12.5 mg every 5 to 9 days. By taking an identical, unmarked capsule each day, the patient would end up receiving sertraline 100 mg/day after 8 weeks. The trial began on Day 1 with a placebo followed by 12.5 mg on Day 6, 25 mg on Day 12, 37.5 mg on Day 18, 50 mg on Day 24, 62.5 mg on Day 31, 75 mg on Day 39, 87.5 mg on Day 48, and 100 mg on Day 57.

The precise timing of the dosage escalation schedule was known only by pharmacy staff. The patient was discouraged from her traditional habit of making written notes of her side effects. As well, office visits were held at 2- to 3-week intervals during the trial, and discussions about medication and side effects were avoided.

At the outset of the trial, the patient was medication-free except for a longtime practice of taking diazepam 5 mg three to four times per week to help her sleep. A Hamilton Rating Scale for Depression (HAM-D) completed by the clinician (J.H.M.) immediately prior to the outset of the trial was scored as 28. At the completion of the trial, the patient reported a significant improvement in her depression and anxiety. She was functioning better socially and at work. The only side effects were mild headache and fatigue. HAM-D scores at Weeks 3, 5, 7, and 10 were 16, 13, 11, and 4, respectively. A 50% reduction in HAM-D score had been achieved by Week 5 of the trial at a corresponding dose of sertraline 62.5 mg/day. At the end of the trial, the patient agreed to proceed with a 6-month period of continuation therapy.

This report confirms that novel approaches to antidepressant administration can be effective in patients who are known to be sensitive to side effects. It is possible that the gradual titration schedule using dosages smaller than what are commercially available and specific behavioral instructions were the relevant factors in the successful outcome. However, the double-blind placebo lead-in approach would have complemented these factors and quite likely contributed to improved compliance. The effect of supportive psychotherapy inherent in this medication trial most likely had minimal impact given this patient's previous exposure to a variety of psychotherapies.

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### Erotomaniac Delusions Focused on a Child

**Sir:** Erotomania is currently classified as a subtype of delusional disorder in DSM-IV and is characterized by a perceived relationship focused more on idealized romantic love and a spiritual union than sexual attraction.<sup>1</sup> Onset generally occurs during early adulthood, and the patient routinely believes that the other person wants to marry him or her. The present case is both striking and unique in that the focus of erotomaniac delusions was a child.

**Case report.** Mr. A, a 29-year-old single man, attributed his difficulties to a girl he met when he was 15. She was 6 then and had moved into his neighborhood. He felt at the time that she "came on" to him and that she was in love with him although there had been no contact, physical or otherwise. He believed she was sending him messages to keep his distance because her mother was protective.

He decided over the next several years that she was the girl he would marry, although he made no effort to pursue the relationship. He remembered wanting to tell a neighbor how he felt about this girl but perceived messages from the mother to stay away. When the girl was 18, he chose to speak to her but was unable to admit his feelings. He felt from that conversation, though, that she wanted to arouse his jealousy, and he believed he "gained a place in her heart" by not acknowledging such feelings.

Shortly after, the mother and daughter moved, and he now sees them only occasionally when they return to visit friends. He has not spoken to her since, although he continues to believe

that she loves him and tries to contact him nonverbally during visits, e.g., "staring at my bedroom window." He has not attempted to contact her and is unaware of her present address.

Clinical assessment indicated no significant medical history or psychiatric illness in the family. Developmentally, Mr. A led a somewhat isolated existence with few friends and no involvement with females in the form of dating or heterosexual relationships. He saw himself as insecure and related this, at least in part, to feeling he was the subject of frequent criticism while growing up. On mental status examination, he described depression related to the frustration of this relationship, but did not meet criteria for a major depressive episode. There was no disorder in thought form. Regarding thought content, he acknowledged referential ideas but did not endorse thought insertion/withdrawal, thought broadcasting, delusions of persecution/grandeur, or perceptual disturbances. No abnormalities were noted in orientation, memory, or concentration. There was no indication of pedophilic interests, and the working diagnosis was delusional disorder, erotomaniac type.

The patient has remained symptomatic despite trials of numerous neuroleptic and antidepressant drugs, including clozapine as well as serotonin selective reuptake inhibitors (SSRIs). However, from the outset, treatment interventions have been compromised by noncompliance.

While there have been reports of erotomania in which the love object was an adolescent,<sup>2,3</sup> to my knowledge this is the first report of erotomaniac delusions focused on a child. Erotomaniac delusions are more commonly seen in females, although they do occur in males and, in these cases, are frequently associated with stalking and/or legal involvement.<sup>2,4</sup> It is therefore fortunate in this case that such activity did not happen. The role of the girl's mother is intriguing, as she was clearly perceived as playing a protective role as the girl grew up. That the patient was not more forceful in his efforts to pursue the relationship is not entirely unusual, and such constraint has been reported in other cases.<sup>5</sup>

Although erotomaniac delusions focused on a child appear rare, this case indicates that children can be the focus of erotomaniac delusions, and clinicians assessing adolescents or adults for inappropriate behavior involving children should be aware of this possibility.

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### Valproic Acid Treatment of AIDS-Related Mania

**Sir:** Mania has been widely reported in human immunodeficiency virus (HIV)-infected patients and has been found to occur at a higher incidence in patients with acquired immune deficiency syndrome (AIDS) during the later stages of cognitive

decline.<sup>1-3</sup> When present, this condition poses significant challenges to the care, safety, and medical management of the patient. Standard treatments of mania, however, are often poorly tolerated in this population.<sup>4,5</sup> Lithium has been found to cause significant neurologic toxicity at therapeutic levels, making it a less attractive choice of treatment, and carbamazepine raises considerable concern because of potential neutropenia. Benzodiazepines may worsen cognitive impairment and lead to further confusion and disinhibition.

Valproic acid has been compared favorably with lithium and carbamazepine and offers an alternative to the treatment of mania in a cognitively impaired, severely physically ill population.<sup>6-8</sup> The following cases demonstrate successful treatment of mania in such compromised patients with valproic acid.

**Case 1.** Mr. A is a 30-year-old white man with AIDS and mild dementia. He was transferred from a nursing home to a psychiatric unit of a university hospital for the treatment of agitation and bizarre behavior. Other symptoms prior to admission included confusion, decreased sleep, and loose, disorganized thinking.

The patient had no past psychiatric history nor did his family. Although Mr. A had a past history of alcohol and cocaine abuse, he was not currently using alcohol or illicit drugs. Medications upon transfer were risperidone, lorazepam, and dapsone. At mental status examination, he was noted to have an elevated mood, increased psychomotor activity, pressured speech, flight of ideas, and grandiose delusions. Neuropsychological testing revealed marked impairment in concentration and cognitive processing speed. Abnormal laboratory values included a WBC of  $2.1 \times 10^9/L$  and a CD4 count of 19 cells/ $\mu L$ . His electrolyte levels and liver function results were within normal limits. An unenhanced head CT scan and an enhanced MRI showed significant atrophy but no focal lesions. An EEG was refused by the patient. The lumbar puncture results were normal. A diagnosis of mood disorder due to AIDS with manic features was made.

At admission to the unit, risperidone and lorazepam were discontinued to simplify Mr. A's medication profile. Perphenazine, which could be used intramuscularly, was titrated to a dose of 16 mg b.i.d. Although his psychotic symptoms decreased, he remained acutely manic without a fluctuating level of consciousness, ruling out delirium. Valproic acid was started and titrated to a blood level of 110  $\mu g/mL$  over 10 days. During this time, the patient demonstrated marked improvement evidenced by resolution of his manic and psychotic symptoms. Valproic acid was tolerated, and no side effects or significant change in his WBC or liver function results was evident. Despite resolution of his acute symptoms, Mr. A continued to have residual cognitive impairment consistent with his underlying dementia and was discharged back to a nursing home facility for supportive care.

**Case 2.** Mr. B is a 39-year-old black man with AIDS and early dementia. He was transferred from a nursing home for increasingly disruptive and disorganized behavior. In the home, he was stealing from other patients, phoning his family at all hours of the night, and was urinating, defecating, and masturbating in public. Other symptoms included agitation and decreased sleep.

Past psychiatric history included an LSD-induced psychosis at the age of 16 years and one other inpatient hospitalization for treatment of psychosis at the age of 20 years. Mr. B had no past history of mania and no family history of mental illness. The patient had a history of cocaine, heroin, and marijuana abuse, but had not used any illicit substances since

placement in the nursing home 6 months earlier. His medications on transfer were molindone 15 mg q.a.m. and 20 mg at bedtime, fluconazole 100 mg q.d., ethambutol 400 mg t.i.d., and Bactrim one tablet three times a week. Mental status examination revealed a man with increased psychomotor activity, pressured speech, elevated mood, irritability, and affect lability. Neuropsychological testing showed poor concentration and impaired cognitive processing speed. Abnormal laboratory values included a WBC of  $0.8 \times 10^9/L$ , CD4 of 0 cells/ $\mu L$ , hemoglobin of 12.8 g/dL, hematocrit of 35.9%, platelets of 194 thousand/ $mm^3$ , chloride of 112 mmol/L, and an alkaline phosphatase of 212 U/L. Head CT results showed atrophy with no focal findings. An EEG was refused by the patient. Lumbar puncture and urine and blood toxicology results were unremarkable. A diagnosis of mood disorder due to AIDS with manic features was made.

At admission, molindone was discontinued, and the patient was started on perphenazine and valproic acid. Small doses of lorazepam i.m. were used as needed for extreme agitation. Valproic acid was titrated to a blood level of 93.8  $\mu g/mL$ , at which point his manic symptoms completely resolved. Perphenazine was gradually discontinued, and Mr. B remained free of mania. There was no evidence of side effects, and the patient was safely returned to the nursing home.

End-stage AIDS presents a complicated picture particularly in the presence of dementia. As cognitive functioning declines, there appears to be a window of time when the onset of mania becomes more likely. Aggressive treatment of this syndrome is critical in maintaining physical stability and safety as well as preserving the provider network caring for the individual in the final stage of life. Treatment can be difficult due to the hypersensitivity to medication side effects and the fragile balance of the immune system. Valproic acid was highly effective and easily tolerated in our patients. In both cases, the problematic behaviors interfering with their living situations were fully managed, and both patients were able to return to their previous familiar placements. Quality of life was preserved and management of their care simplified. Further studies on the course of this syndrome and the long-term effects of valproic acid in this population would be helpful given the rare occurrence of thrombocytopenia, elevated liver functions, and pancreatitis with this medication.

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