

LETTERS TO THE EDITOR

Neuroleptic-Induced Tardive Dyskinesia

TO THE EDITOR: Greater risk of tardive dyskinesia has been linked to cumulative neuroleptic exposure and early development of extrapyramidal side effects (1). Risperidone is a putatively "atypical" antipsychotic with a relatively low prevalence of extrapyramidal side effects at therapeutic doses (2). Fluoxetine and other agents that selectively inhibit presynaptic reuptake of serotonin may exacerbate motor symptoms when given in combination with antipsychotic medication (3). We describe a patient who developed extrapyramidal side effects that were followed by dyskinetic tongue movements in association with combined fluoxetine and risperidone treatment.

Mr. A, an 18-year-old white man, had been treated for putative attention deficit disorder with hyperactivity with methylphenidate (maximum dose was 75 mg/day) for 7 years. Methylphenidate treatment was permanently discontinued because of the onset of persistent psychotic symptoms (the condition was ultimately diagnosed as chronic undifferentiated schizophrenia). Treatment ensued with successive regimens of thioridazine (maximum dose=50 mg/day; duration=2.5 weeks), trifluoperazine (maximum dose=3 mg/day; duration=5 months), fluphenazine (maximum dose=10 mg/day; duration=5 weeks), and risperidone (maximum dose=4 mg/day; duration=2 weeks). The neuroleptic regimen was changed frequently because of dose-limiting extrapyramidal side effects and sedation.

For 3 months, Mr. A was taking fluoxetine, 20 mg/day, but no antipsychotic medication. During this interval, a neurologist, an internist, and a psychiatrist administered a neurological examination and found no motor abnormalities. Mr. A was treated with a combined regimen of risperidone, 2–3 mg/day, and fluoxetine, 20 mg/day, for over 4 months. Extrapyramidal symptoms were first noted 1 week after initiation of risperidone. Three months later, involuntary, repetitive, sinuous, rolling, dyskinetic tongue movements of mild-to-moderate intensity, as well as very mild masticating movements, were noted over several weeks by the family and the attending psychiatrist, consulting psychiatrist, and consulting neurologist. A consensus diagnosis of probable neuroleptic-induced tardive dyskinesia was reached. The risperidone and fluoxetine regimens were discontinued, and an investigational protocol was initiated with another putative atypical antipsychotic agent that was felt to have low extrapyramidal side effect liability. The dyskinetic movements persisted unchanged for over a week. Subsequent observation over the next 4 months revealed the movements to be much attenuated and present only intermittently. Results of oral, physical, and neurological examinations, a computerized axial tomography scan of the head, antinuclear antibody titer, urine drug screen, and tests of thyroid, hepatic, renal, and hematological function were normal. Analysis of erythrocyte sedimentation rate, 24-hour urine for heavy metals, and serum copper and ceruloplasmin levels revealed no abnormality. There was no history of substance abuse. Family history was noteworthy for mood disorder.

The single case we report is of heuristic value only. Interpretation is confounded by the potential drug interaction. There has been insufficient duration of experience with risperidone to empirically test the hypothesis that its relatively low prevalence of extrapyramidal side effects will ultimately be associated with a relatively low prevalence of tardive dyskinesia.

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Risperidone-Induced Tardive Dyskinesia

TO THE EDITOR: Minimal extrapyramidal side effects (which represent a possible risk factor for the development of tardive dyskinesia [1]) have been reported with risperidone treatment in doses up to 6 mg/day (2). Risperidone may also have antidyskinetic effects in doses of 6–16 mg/day (3). My colleagues and I recently treated a patient who experienced a recurrence of tardive dyskinesia during treatment with risperidone.

Ms. A was a 46-year-old Hispanic woman with moderate mental retardation of unknown etiology, mild systemic lupus erythematosus that was in remission, and a 30-year history of rapid-cycling bipolar mood disorder. She had an excellent but transient response to two courses of ECT about 30 years earlier, and various neuroleptic regimens combined with lithium had proven partially helpful about 10 years earlier. Disfiguring oral-facial-lingual dyskinesia developed after decades of neuroleptic treatment but completely resolved after the antipsychotic medications were withdrawn. She had been euthyroid and without dyskinetic movements for 10 years when she suffered a recurrence of her psychotic mood disorder that proved refractory to lithium combined with carbamazepine, valproic acid, and levothyroxine sodium (all at therapeutic blood levels).

Risperidone was added to a regimen of controlled-release lithium carbonate, 900 mg/day; carbamazepine, 800 mg/day; levothyroxine, 25 µg/day; and vitamin E, 1600 IU/day. The risperidone dose was gradually increased over 3 weeks to 3 mg b.i.d., at which time her mood, sleep pattern, rate of speech, coherence of thought, and capacity to follow directions began to normalize. One week later, however, Ms. A developed a severe dyskinesia that consisted of chewing movements, a vermicular tongue motion that was visible under her jaw even when her mouth was closed, lip smacking, tongue protrusions ("fly catcher's tongue"), and rapid eye blinking. Her trunk and extremities were uninvolved, and there was no cogwheel rigidity or tremor observed in her limbs. Her risperidone dose was tapered and discontinued over 1 week; her dyskinetic movements completely resolved within 2 weeks after the risperidone treatment ended.

We have searched the literature and believe that this is the first published case of risperidone-associated tardive dyskinesia. While this patient experienced what might be considered an acute dyskinesia, the symptoms were identical to the tardive dyskinesia that had developed 10 years earlier after years of neuroleptic treatment. The rapidity of recurrence is consistent with our experience in other patients with resolved tardive dyskinesia who, when rechallenged with neuroleptics, rapidly developed a movement disorder that was identical to

the disorder that prompted the initial discontinuation of the neuroleptic.

Although lupus can cause dyskinesias (4), the temporal relationship between the patient's symptoms and risperidone treatment and the fact that lupus was clinically quiescent would argue against lupus as the cause of dyskinesia in this case.

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Risperidone and Bullous Pemphigoid

TO THE EDITOR: Risperidone, a novel antipsychotic, is a benzisoxazole derivative that displays antagonism of central serotonin (5-HT₂) receptors at low doses and potent antagonism of dopamine (D₂) receptors at higher doses (1). It has a favorable side effect profile, including a low risk of extrapyramidal side effects. Clinical experience remains limited, and we report here a dermatological complication of risperidone usage.

Mr. A was a 74-year-old Caucasian man who was admitted to the hospital because of a 12-month history of visual hallucinations (e.g., he would make cups of tea for "visitors" to his home). Over the previous several years, there had been a history of worsening memory, disorientation, and confusion. His only medical problem was Parkinson's disease, which had been diagnosed 6 years earlier and was being treated with a regimen of levodopa and carbidopa; he was taking no other medication. A physical examination revealed an akinetic-rigid syndrome. He scored 16 out of 30 on the Folstein Mini-Mental State examination. A routine pathologic examination failed to uncover any acute hematological, biochemical, metabolic, or infectious abnormalities that might have caused delirium. A diagnosis of dementia, of either Alzheimer's or Lewy body (2) type, was made. In the hospital, Mr. A became suspicious and began to experience auditory hallucinations, and there was a concomitant disturbance in his behavior. Because it was relatively unlikely to lead to a worsening of his parkinsonism, risperidone was prescribed and was increased cautiously to 4 mg/day. Thirteen days after commencement of risperidone treatment, Mr. A developed on his forearms a bullous eruption on a background of erythematous skin that was consistent with pemphigoid. He had no previous history of any skin disease, and there had been no other changes in his regular medications or diet. Risperidone therapy was stopped, and treatment with prednisolone, 30 mg/day, and azathioprine, 50 mg/day, commenced. This regimen led to substantial improvement but incomplete resolution of the bullae.

While skin disturbances have been reported with antipsychotic treatment (3), we are unaware of any previous reports of an association between risperidone and pemphigoid. Since about 80% of patients who develop pemphigoid are over the age of 60 (4), it is of concern that preclinical testing of risperidone involved seven multicenter trials of schizophrenic patients who were under the age of 65 (5). However, the product has been licensed for use in the elderly, a group in whom the pharmacokinetics, pharmacodynamics, and indications for use tend to be different. Therefore, we urge caution in the use of this and other novel antipsychotic medications in the elderly, especially with respect to potential side effects.

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Agranulocytosis After Addition of Risperidone to Clozapine Treatment

TO THE EDITOR: Various severe adverse effects have been reported when clozapine has been used in combination with other psychotropic medications. Respiratory depression has been associated with concomitant benzodiazepine and clozapine use (1), while neuroleptic malignant syndrome has been described when clozapine was combined with lithium (2) or carbamazepine (3). Agranulocytosis has been reported in patients simultaneously treated with clozapine and traditional antipsychotics (4). We report a patient who precipitously developed agranulocytosis after risperidone was added to a stable regimen of clozapine.

Ms. A was a 33-year-old woman who met DSM-IV criteria for schizoaffective disorder. Her numerous traditional antipsychotic trials were unsuccessful and resulted in severe tardive dystonia. Her most recent treatment trial was a 22-month regimen of clozapine that had been kept at a stable dose of 900 mg/day for the last 7 months. She then required psychiatric hospitalization, and 4-6 mg/day of risperidone was added to her clozapine regimen. All other medication regimens had been stable for several months; these consisted of lithium, 1200 mg/day, and numerous medications for her severe tardive dyskinesia (diphenhydramine, 300 mg/day; trihexyphenidyl, 4 mg/day; clonazepam, 4 mg/day; and vitamin E, 400 IU/day).

During the 22 months that Ms. A was taking clozapine, she had had no episodes of neutropenia or leukopenia (her WBC count was generally between 5,000/mm³ and 8,000/mm³). Six weeks after risperidone was added to her treat-