

Letters to the Editor

Seizure During Risperidone Treatment in an Elderly Woman Treated With Concomitant Medications

Sir: Risperidone, a recently introduced novel antipsychotic, is associated with a low incidence of seizures. During premarketing testing, seizures occurred in 0.3% (9/2607) of risperidone-treated patients (with dosages unrevealed), two in association with hyponatremia.¹ To our knowledge, no post-marketing risperidone-associated seizure has been reported. We describe an elderly schizophrenic woman who developed a single seizure after 2 days of coadministration of risperidone, sulfamethoxazole-trimethoprim, and astemizole.

Case report. Ms. A, a 64-year-old Chinese schizophrenic woman, had been physically healthy and devoid of any seizure or substance abuse history before this hospitalization. She failed adequate trials of two antipsychotics, sulpiride and flupenthixol. After 7 days of washout, risperidone was started at 1 mg b.i.d. on Day 1. However, a mild urinary tract infection occurred incidentally on the same day. Sulfamethoxazole (400 mg)-trimethoprim (80 mg) was thus coadministered b.i.d. On Day 2, the dosage of risperidone was increased to 2 mg b.i.d. A mild scalp itch appeared, and astemizole 10 mg/day was then prescribed. Surprisingly, 9 hours after taking the initial four doses (1 mg, 1 mg, 2 mg, and 2 mg) of risperidone, she experienced a single, witnessed, 1-minute generalized tonic-clonic seizure with a 5-minute postictal confusion period. Risperidone was discontinued immediately, and astemizole was withdrawn 1 day later. Sulfamethoxazole-trimethoprim was continued for 7 days. A thorough workup, including urine/blood routine, a biochemistry examination, an ECG and a head CT scan, produced negative findings, except bacteriuria and a mild fever. The electroencephalogram results before risperidone therapy and 1 day and 4 months after the seizure were all unremarkable. Her psychotic symptoms (e.g., auditory hallucinations) subsided abruptly after the seizure, but emerged again 15 days later. Consequently, risperidone was restarted at a lower dosage, 0.5 mg h.s., and was titrated over 2 days to 0.5 mg b.i.d. The psychotic symptoms receded on this regimen. She has now been free of seizures for 4 months. Antiseizure medications were not added.

Astemizole, a peripherally acting H₁ antagonist, has not been reported to induce seizures in patients. In developing mice, astemizole, in contrast to other centrally acting H₁ antagonists, does not increase the durations of electrically induced seizures.² Rare incidences of convulsions have been indicated in sulfamethoxazole-trimethoprim-treated patients.³ However, among 1121 sulfamethoxazole-trimethoprim-treated inpatients participating in the Boston Collaborative Drug Surveillance Program, none developed seizures.⁴ Drug-drug interactions have not yet been reported among risperidone, astemizole, and sulfamethoxazole-trimethoprim. Studies to investigate the possibilities of their drug interactions are needed in the future.

The initial risperidone dosing schedule of the present case had been used in the North American multicenter studies with the subjects aged 18–65 years.^{5,6} Nonetheless, there is a paucity of data relating to the use of risperidone in elderly schizophrenic

patients.^{7,8} Of the very few geriatric subjects in the previous open trials, most could tolerate the final daily doses of 4–6 mg with slower dose increments.^{7,8} In the elderly, the half-lives of risperidone and its active metabolite, 9-hydroxyrisperidone, are prolonged; and the clearance of 9-hydroxyrisperidone is reduced.⁹ Therefore, larger-scale and well-designed studies regarding the optimal dosing strategy (in terms of both efficacy and adverse drug effects) in geriatric schizophrenics are required.

Due to ethical issues, a rechallenge with the initial dosing schedule was not applied to this patient. Nevertheless, the potentially contributory role of risperidone in the seizure should be considered. High-dose therapy and rapid upward dose titration are associated with greater risks of seizures in patients treated with classical antipsychotics¹⁰ or clozapine¹¹; and, accordingly, might also increase the potential of risperidone-related seizures. This patient, experiencing no seizures on the second occasion of risperidone treatment (with lower doses and slower dose titration), might lend partial support to this presumption. To prevent dose (and dose increment)-related side effects, such as postural hypotension and possible seizures, we now recommend the guideline of “start low and go slow” for risperidone therapy in the elderly,^{9,12,13} especially those with impaired kidney or liver functions^{9,12,13} or those using concomitant medications that could affect the metabolism of risperidone.^{12,13}

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Valproate Monotherapy in an SRI-Intolerant OCD Patient

Sir: Many patients with obsessive-compulsive disorder (OCD) considered to be treatment refractory have prematurely discontinued serotonin reuptake inhibitors (SRIs) due to side effects (such as irritability and anxiety) and are not truly treatment refractory. Some OCD patients intolerant of SRIs had decreased adverse effects after pretreatment with valproic acid.¹ We therefore pretreated an OCD patient intolerant of standard doses of fluoxetine, sertraline, and clomipramine with valproic acid.

Case report. Mr. A, a 35-year-old single white man with a 15-year history of OCD, had stopped his job as a mechanic because of increased anxiety and marked obsessions about his parents' safety. He compulsively touched his parents 70 to 80 times per day, checking that they were alive. Mr. A became housebound and prevented his parents from answering phone calls out of obsessional fears, which he acknowledged were senseless. His mood was sad without neurovegetative symptoms. He had a family history of depression, with good treatment response to conventional antidepressants, but no family history of bipolar disorder or treatment with mood stabilizers. Baseline ratings revealed Yale-Brown Obsessive Compulsive Scale (Y-BOCS), Hamilton Rating Scale for Anxiety (HAM-A), and Hamilton Rating Scale for Depression (HAM-D) scores of 24, 9, and 20, respectively.

We started fluoxetine 5 mg/day, which Mr. A discontinued on his own because of feelings of anxiety and agitation. We then started low-dose valproic acid (250 mg t.i.d.), intending to reintroduce fluoxetine later. Although his anxiety decreased, he discontinued valproic acid because of sedation after 1 week. Valproic acid was restarted (250 mg q.a.m., 500 mg q.h.s.), together with fluoxetine 1 mg/day. Two weeks later, he appeared less anxious, "in control," and had resumed working 5 to 10 hours/day after not working for 6 months. His obsessions regarding his parents' safety ceased. His total Y-BOCS, HAM-A, and HAM-D scores decreased to 11, 6, and 12, respectively. His plasma valproic acid level was therapeutic at 85 µg/mL. Although we originally planned to increase the fluoxetine dose, we discontinued it instead, believing valproic acid was responsible for the clinical improvement. The patient further improved on valproic acid monotherapy: his overall Y-BOCS, HAM-A, and HAM-D scores decreased to 8, 3, and 10, respectively. This apparent antiobsessional and antidepressant effect of valproic acid has continued for 10 weeks. His OCD symptoms are now mild, and he reports euthymic mood. He has resumed a normal work schedule, and his social interactions have improved.

This case suggests that valproic acid monotherapy may be useful in OCD patients who are intolerant of SRIs. The maximum beneficial valproic acid effect in this patient occurred only

after therapeutic levels of the drug were achieved. The patient may have benefited from valproic acid treatment because of comorbid depression, although OCD appears to be his primary diagnosis. There is evidence that clonazepam may be useful in augmenting SRI treatment in OCD,² possibly implicating GABAergic mechanisms, which may account for therapeutic effects of valproic acid in this case. Controlled clinical trials are needed to establish the effectiveness of valproic acid monotherapy in OCD and other anxiety disorders.

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Risperidone and Allergic Reactions

Sir: Risperidone, the first benzisoxazole antipsychotic, has dopamine D₂ and serotonin 5-HT₂ antagonistic properties. To our knowledge, there have been only three case reports¹⁻³ regarding dermatologic side effects of risperidone. Two of the patients^{1,3} suffered from edema, and the third² had bullous pemphigoid. In this report, we present a case of severe allergic reactions to risperidone resulting in edema, eruption, and stridor.

Case report. Mr. A, a 67-year-old man with epileptic psychosis, had been treated with the same combination of carbamazepine, phenytoin, phenobarbital, haloperidol, profenamine, idebenone, vinpocetine, and diltiazem for several years. The types and dosages of these medications were unchanged during the addition of risperidone and subsequent allergic reactions.

Because a thought disorder (i.e., loosening of association) persisted, 2 mg/day of risperidone was added in 1996 and was increased gradually to 6 mg/day over 2 weeks. One month after the start of risperidone treatment, he developed edema on his face and both insteps. At that time, his renal function, thyroid function, and serum total protein were within normal range. Risperidone was discontinued 42 days after its start. No changes were made in the other drugs. Antihistaminergic treatments were started; however, he developed disseminated maculopapular drug eruption 1 day after the discontinuation of risperidone and stridor 4 days after discontinuation. The eruption had urticarial character. Seven days after discontinuation, the edema, eruption, and stridor persisted, and IgE was elevated at 261 IU/mL (normal range, < 250 IU/mL), whereas C3 and C4 were 101 mg/dL (normal, 55-115) and 29.7 mg/dL (normal, 15.0-50.0), respectively. After 15 days, the edema had resolved completely, both the eruption and stridor had improved, and IgE was decreased to 205 IU/mL. After 21 days, the disseminated maculopapular eruption and stridor had also resolved completely.

In this case, the edema occurred 31 days after the commencement of risperidone and lasted 26 days, while the eruption and stridor began 43 and 46 days after starting risperidone

and lasted 20 and 17 days, respectively. Although the eruption and stridor occurred just after risperidone discontinuation, it seems likely that risperidone and/or its active metabolite, 9-hydroxyrisperidone, remained in the patient's body and induced the eruption and stridor. Strictly speaking, however, it is not clear whether risperidone itself or the other components in the tablet contributed to Mr. A's allergic reactions. It is thus worth noting that the Japanese version of the risperidone tablet includes wax in place of the pigment found in the U.S. tablet.

With regard to the types of allergic reactions, Type I allergic reaction may be plausible because IgE was elevated, albeit slightly, during these reactions. Stridor is common in Type I allergic reaction, and the eruption was urticarial in character, whereas Type II and Type III reactions are somewhat unlikely because C3 and C4 values were within normal range. Other reactions, such as Type IV, might also be considered because it took a relatively long time for Mr. A's allergic reactions to occur after he started taking risperidone and to resolve after he stopped taking risperidone.

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Delirium With Manic Symptoms Induced by Diet Pills

Sir: We report on a patient with chronic depression controlled by antidepressant medication who developed delirium with manic symptoms after being started on diet pills containing a combination of fenfluramine and phentermine.

Case report. Ms. A, a 50-year-old overweight white woman with a history of major depression, had been stable on a combination of imipramine 150 mg q.d. and venlafaxine 100 mg b.i.d. for more than 2 years with no adverse reactions. Two weeks before hospitalization, the patient's internist prescribed diet pills consisting of fenfluramine 20 mg t.i.d. and phentermine 30 mg q.d. On Day 10 of the diet pill regimen, Ms. A became manic with elated mood, increased psychomotor activity, decreased sleep, racing thoughts, pressure of speech, and loosening of association. She was also hypersexual and appeared confused at times, but had neither grandiose delusions nor hallucinations. She had no past history of mania or family history of bipolar disorder.

Ms. A was brought to the emergency room and, after initial evaluation, was admitted to the medical floor. Her mental status examination showed impaired recent memory, loosening of association, and an irritable affect. Physical examination results were normal, and all routine laboratory test results were within normal limits except for an elevated WBC count. No evidence of infection was found on blood cultures, chest x-ray, and CSF analysis. A CT scan of the brain showed no abnormalities.

While Ms. A was on the medical floor, both psychotropic medication and the diet pills were withdrawn. The manic symp-

toms and the cognitive deficits remitted by the third day of hospitalization, at which time she was transferred to the psychiatric floor. She was restarted on antidepressants and observed for 5 days. The patient remained asymptomatic during the rest of her stay.

The prevalence of obesity in the United States has increased in the last few decades; around 30% of U.S. adults are considered overweight.¹ Obesity contributes to many adverse health outcomes, such as cardiovascular disease, diabetes mellitus, and cancer.² While earlier treatments for obesity consisted mainly of diet control and behavior modification, pharmacotherapy has gained immense popularity after the recent reports by Weintraub et al.^{3,4} that showed sustained weight loss with a combination of fenfluramine and phentermine. This increased popularity has led to the establishment of many weight loss clinics devoted to the prescription of weight loss pills such as fen-phen and dexfenfluramine.

The rationale for using a combination therapy is that drugs with different mechanisms of action used together in smaller amounts provide equal or greater efficacy with fewer adverse effects than the same drugs used in monotherapy at higher doses. Fenfluramine acts by a serotonergic mechanism, whereas the stimulant anorexiant phentermine appears to decrease appetite through a dopaminergic and noradrenergic pathway.⁵ Although this combination has been relatively well tolerated, we report a case of diet pill-induced delirium with manic symptoms in a patient with a long-standing history of depression. These diet pills may cause sufficient imbalance in the neurotransmitters or their receptors to result in cognitive and mood disturbances in predisposed individuals. Thus, it may be necessary to exercise caution while prescribing these diet pills in individuals with a prior history of mood disturbances.

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Editor's Note: The letter by Drs. Bagri and Reddy was submitted before fenfluramine was withdrawn from the U.S. market.

Rapid Efficacy of Olanzapine Augmentation in Nonpsychotic Bipolar Mixed States

Sir: Traditional antipsychotics are potent acute antimanic agents. However, their utility is limited by acute and chronic neurologic toxicity, which appears to be more prevalent in mood disorder than in schizophrenia patients.^{1,2} In addition, in

some patients older antipsychotics may either exacerbate or fail to relieve or to prevent depressive symptoms.

The introduction of atypical antipsychotics with less potential for neurologic adverse effects and greater potential for relief of negative symptoms (which resemble depression) has led to preliminary clinical exploration of the roles of such agents in the management of patients with both psychotic and nonpsychotic bipolar disorders. Clozapine appears to stabilize mood,³ while risperidone may yield a complex pattern of alleviating depression⁴ as well as mania^{4,5} in some patients yet exacerbating or inducing mania^{6,7} in others. The latter profile to some extent resembles that of an antidepressant (rather than a mood stabilizer) and could be due to the predominant serotonin 5-HT₂ receptor antagonism seen with risperidone.

Olanzapine is a recently marketed atypical antipsychotic with a safety profile superior to that of clozapine. Emerging evidence suggests that olanzapine may relieve mood symptoms in patients with schizophrenia, schizoaffective disorder, and psychotic mood disorders.⁸⁻¹¹ Olanzapine has a receptor antagonism profile more like that of clozapine than that of risperidone.¹² In particular, olanzapine lacks the predominant 5-HT₂ receptor blockade seen with risperidone. Thus, olanzapine could provide less risk of mania, mixed states, or rapid cycling than risperidone. We present our experience with our first two bipolar patients treated with olanzapine. These bipolar I patients with nonpsychotic mixed states (as diagnosed using DSM-IV criteria) had rapid dramatic improvement with the addition of olanzapine to mood stabilizers.

Case 1. Mr. A, a 34-year-old married Asian male professional, has had bipolar I disorder since age 17 and prior but not current drug and alcohol abuse. He was hospitalized once for nonpsychotic mania, and, on lithium monotherapy, he had a 2-month mixed mood state episode and required intermittent antidepressant or thioridazine for subsyndromal depressive and hypomanic symptoms, which initially resolved with the addition of divalproex sodium.

However, after a 4-month period of euthymia while taking lithium 900 mg/day (serum level = 0.7 mEq/L) and divalproex sodium 750 mg/day (serum level = 51 µg/mL), and during a period of increased occupational and familial stress, Mr. A entered a nonpsychotic mixed mood state that gradually worsened over a 6-week period. Symptoms included marked irritability (he had not talked to his wife for several days), psychomotor agitation, distractibility (he stopped driving after a minor motor vehicle accident), episodic passive suicidal ideation, and decreased sleep (4 hours), need for sleep, appetite, and ability to enjoy activities. He denied psychotic symptoms, but admitted marked pessimism regarding the chances of survival of his marriage, despite the repeated assurances of his distraught wife that she was firmly committed to their relationship. Hospitalization was offered, but Mr. A and his wife expressed a strong desire to address these difficulties with outpatient treatment.

Doses of lithium and divalproex had previously been limited by gastrointestinal (diarrhea) and neurologic (tremor) adverse effects. Thus, olanzapine 10 mg at bedtime was added, and the patient slept well after the initial dose for the first time in over 2 weeks. On awakening the next morning, he reported complete remission of symptoms, and thus hospitalization was avoided. His wife even expressed some anxiety around how suddenly his mood had completely returned to euthymia. He experienced very mild sedation on first awakening in the morning, which resolved after 3 days of therapy, but denied any other adverse effects. Six months later, Mr. A continues improved, and a gradual taper of olanzapine will be considered once the ongoing occupational and familial stressors resolve.

Case 2. Ms. B, a 47-year-old married white female professional, has had bipolar I disorder since age 22 and abused drugs in her early 20s. She had never been psychotic or hospitalized, but manic episodes had resulted in job loss and marked relationship difficulties. In the prior year she had been rapidly cycling between major depression and hypomania despite taking carbamazepine 800 mg/day (serum level = 8.4 µg/mL) and levothyroxine 100 µg/day and minimizing antidepressant (paroxetine and bupropion) use.

Carbamazepine was discontinued due to neurotoxicity and inefficacy. Over a 2-week period while being switched from carbamazepine to divalproex sodium, Ms. B escalated into a mixed mood state with marked affective lability. Her mood gradually shifted from predominantly euphoric with very brief periods of irritability and depression (particularly during interactions with her husband) to irritable and dysphoric most of the time and in most social interactions with only brief periods of euphoria. She developed decreased sleep (3 hours) and need for sleep and variable appetite along with psychomotor agitation, distractibility, and passive thoughts of death, but no psychotic symptoms. She took medical leave from work, and problems at home intensified so that her husband considered moving out of the house. The above occurred despite therapy with divalproex sodium 375 mg/day, lorazepam 3 mg/day, and levothyroxine 100 µg/day. Both the patient and her husband agreed to having her admitted to the hospital.

In view of gastrointestinal discomfort (diarrhea), which was limiting the rate of divalproex introduction, and Ms. B's psychiatric acuity, olanzapine 10 mg at bedtime was added, and that night she slept well for the first time in 10 days. Her mood was improved the next morning, but she complained of sedation and light-headedness, which attenuated enough the following day to allow discharge home with partial (day) hospitalization. Thus, full (inpatient) hospitalization was limited to 2 days. Her husband felt she had improved sufficiently that he no longer wished to move out.

Over the next 2 weeks during partial hospitalization, medications were gradually titrated so that, on lithium 600 mg/day (serum level = 0.5 mEq/L), divalproex sodium 750 mg/day (serum level = 59 µg/mL), and levothyroxine 100 µg/day, her mood improved further, she returned to work, and olanzapine could be subsequently decreased to 5 mg at bedtime. Two weeks later, scheduled dosing of olanzapine was discontinued. For the following 4 months, Ms. B remained primarily euthymic with baseline occupational and social function. However, efforts to decrease mood stabilizer doses to improve gastrointestinal tolerability yielded breakthrough mood symptoms and insomnia, which were alleviated by 2.5 to 5 mg of olanzapine at bedtime as needed.

These cases demonstrate that addition of olanzapine to mood stabilizers in patients with nonpsychotic bipolar mixed states may yield rapid affective improvement and may be well tolerated. It is not clear whether olanzapine yielded direct mood stabilization or indirect benefit by improving sleep. Hospitalization was avoided in one case and limited to only 2 days in the other. Thus, olanzapine augmentation appeared to limit not only patient suffering, but also hospitalization costs.

Our two open treatment cases need to be considered with caution, particularly in view of the early positive experience with risperidone, which was later qualified with the possibility that this agent may induce or exacerbate mania in some patients.⁴⁻⁷ However, mixed states are among the most difficult treatment challenges in bipolar disorders, and this very limited initial experience suggests that further clinical exploration and ultimately controlled trials may be warranted to examine the

efficacy and tolerability of olanzapine in patients with bipolar disorders, even in the absence of psychotic symptoms.

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Mania Induced by Risperidone: Dose Related?

Sir: Risperidone is a serotonin-2/dopamine-2 (5-HT₂/D₂) receptor antagonist that has demonstrated efficacy in the treatment of schizophrenia. It has also been suggested to possess acute antimanic effects in some patients.¹ Other preliminary data, however, indicate that risperidone may initiate or exacer-

bate manic symptoms owing to its putative antidepressant activity.²⁻⁶ The mixed data (and the underlying etiologies) on its mood effects need to be clarified. We here report two schizophrenic patients who developed manic symptoms at specific doses of risperidone, but not at other doses. We propose a potential mechanism to account for this probable dose-related phenomenon as well as the prior inconsistent reports concerning risperidone's mood effects.¹⁻⁶

Case 1. Ms. A, a 48-year-old Chinese woman, had suffered from schizophrenia for 10 years without treatment. She had been physically healthy and devoid of any seizure or substance abuse history. Recently, she was first hospitalized for acute exacerbation with prominent positive and negative symptoms, including auditory hallucinations, persecutory delusions, somatic delusions, apathy, alopecia, anergia, and anhedonia. Physical examinations, ECG, chest x-ray, urinalysis, hematology, serum chemistry, and hepatitis B serology all produced negative findings.

Risperidone alone was initiated and gradually titrated to 6 mg/day over 3 days. Adverse drug effects, including sinus tachycardia, dizziness, acute tongue dystonia, tremor, and sialorrhea, developed without reductions in the positive and negative psychotic symptoms. Three weeks later, the dosage was reduced to 4 mg/day because of the intolerable adverse effects. The positive symptoms subsided; however, the negative symptoms and the side effects continued. Consequently, we further decreased the dosage to 3 mg/day after 2 more weeks. A manic state with grandiosity, hyperactivity, increased talkativeness, flight of ideas, and elated mood emerged 2 days later.

The EEG performed 4 days after the initial presentation of manic symptoms showed generalized intermittent theta waves and generalized spike-and-wave complexes. To prevent potential seizures, risperidone was withdrawn temporarily. The manic features receded soon, and the positive and negative psychotic symptoms recurred. A normal EEG pattern returned 9 days after risperidone was discontinued. We thus restarted risperidone at 2 mg/day. A hypomanic state with pressured speech, hyperactivity, increased appetite, and euphoric moods came back within 2 days. The EEG displayed generalized intermittent theta waves. The dose was then tapered to 1.5 mg/day. Three days later, the positive and the negative psychotic symptoms as well as the adverse drug effects diminished greatly. A euthymic mood resumed, and EEG results were normal.

Case 2. Mr. B, a 36-year-old Chinese man with chronic schizophrenia, was hospitalized for auditory and somatic hallucinations and persecutory delusions. Neither comorbid medical conditions nor substance abuse was noted. He was prescribed risperidone after failure to respond to four classes of traditional antipsychotic drugs. The dosage was titrated up to 6 mg/day in 3 days. After 6 more days, the psychotic symptoms receded, but severe akathisia emerged even after the gradual addition of benztropine up to 6 mg/day over another 3 days. After 5 more days, the dose of risperidone was decreased to 4 mg/day. The akathisia lessened, but a manic state appeared 3 days later. Euphoric mood, hyperactivity, pressured speech, flight of ideas, and grandiosity were evident over the next 10 days. The risperidone dosage was further reduced to 2 mg/day. Mr. B then became euthymic and free from psychotic symptoms and side effects. No other concomitant medications were prescribed.

At least two treatment-related factors could have affected the development of mania in our two patients: the dose before the manic features and the treatment duration after risperidone was initiated. First, it is possible that the mania might appear at specific doses; doses that are too high or extremely low may be

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