Alendronic Acid for Antipsychotic-Related Osteopenia

TO THE EDITOR: Hyperprolactinemia is associated with osteopenia and osteoporosis (1). Antipsychotics can cause persistent hyperprolactinemia and menstrual disturbance (2). We report an association of antipsychotic treatment, hyperprolactinemia, and osteopenia and describe the patient's response to bisphosphonate treatment.

Ms. A was a 58-year-old woman with paranoid schizophrenia. She had received trifluoperazine, 10 mg/day, for 2 years, followed by a depot injection of haloperidol decanoate, 125 mg every 2 weeks, for the past 12 years. After starting the haloperidol depot, she was amenorrheic for 18 months. Her periods were then regular until menopause, which occurred 7 years before she was seen. She was taking procyclidine, 5 mg/day, for mild extrapyramidal symptoms and had been stable since her only hospital admission 12 years ago.

Our medication review service gave Ms. A a systematic evaluation of symptoms, side effects, and physical health. The assessment showed a mildly elevated prolactin level (505 mIU/ml, upper limit of normal=450 mIU/liter). Her gonadal hormone levels were consistent with her postmenopausal status (estradiol, 44 pmol/liter; follicle-stimulating hormone, 54 IU/liter; luteinizing hormone, 30.9 IU/liter; progesterone, 1.08 nmol/liter).

In view of her hyperprolactinemia, Ms. A's bone mineral density was evaluated with a dual X-ray absorptiometry scan of her lumbar spine and hip. Her spine and hip t scores were –2.02 and –1.74, respectively, both indicating osteopenia and an increased risk of fracture (3). Her age-corrected scores were low, at –0.67 (spine) and –0.84 (hip), compared to normal values of 0. She was uniparous and had never smoked or breast-fed. Her diet typically included 500 mg/day of calcium. She performed 140 minutes of weight-bearing exercise per week. There was no personal or maternal history of bone fracture or medical conditions.

Ms. A did not wish to change antipsychotic treatment, citing its convenience. She began taking alendronic acid, 5 mg/day, to treat her osteopenia. A dual X-ray absorptiometry scan at 1 year showed that her spine and hip t scores had improved by 7% and 9% to –1.87 and –1.58, respectively. Her prolactin level remained mildly elevated.

Hyperprolactinemia, hypogonadism, and amenorrhea are major risk factors for low bone mineral density (3). Our patient experienced antipsychotic-induced amenorrhea and hyperprolactinemia. The hormonal side effects of antipsychotics may have contributed to the osteopenia in this case, although other factors cannot be excluded. This case highlights several issues. Stable patients may experience undetected side effects with significant health consequences. Medication review programs may ameliorate this risk. High rates of hyperprolactinemia (75% of women, 35% of men), hypogonadism (65% of women, 6% of men), and menstrual disturbance (65% of women) are reported in patients taking antipsychotics (2, 4). Some antipsychotics, such as clozapine, olanzapine, and quetiapine, show less prolactin elevation and may be a treatment option (5). Alternatively, the dose of the antipsychotic could be lowered. For antipsychotic-treated patients with osteopenia for whom changes in medication are unadvised, the addition of a bisphosphonate offers a successful treatment option.

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Extrapyramidal Syndrome and Long-Acting Injectable Risperidone

TO THE EDITOR: The following are reports of three male inpatients who developed extrapyramidal symptoms within 24 hours of an injection of depot risperidone. All three men met DSM-IV criteria for schizophrenia.

Mr. A, a 32-year-old man, had been taking 15 mg/day of olanzapine for the last 4 months. Because of a long history of poor adherence to treatment in the community, we prescribed a depot antipsychotic. Injectable risperidone, 25 mg, was given while Mr. A was taking 15 mg/day of olanzapine. Twenty-four hours after the injection, he developed oculogyric crisis, dysarthria, torticollis, dysphagia, tremor, and rigidity. These symptoms responded to procyclidine.

Mr. B, a 36-year-old man, was taking depot zuclopenthixol decanoate, 400 mg every 2 weeks, for 12 months. Because of extrapyramidal side effects, we decided to change the zuclopenthixol decanoate to injectable risperidone. Instead of his regular depot treatment, Mr. B received 25 mg of injectable risperidone. Twenty-four hours later, his extrapyramidal symptoms worsened. These symptoms remitted in 1 week without specific treatment.

Mr. C, a 28-year-old man, was taking olanzapine, 20 mg/day, for 4 weeks. Because of a long history of poor adherence to treatment in the community, we decided to offer depot medication. Olanzapine was reduced and finally stopped within 1 week. After that, we began treatment with oral risperidone and reached 4 mg/day in 3 days. The next day, a few hours after the injection of 25 mg of risperidone, Mr. C developed akathisia, which responded to lorazepam.

The development of extrapyramidal symptoms within 24 hours of administering the depot was not expected. Despite adherence to current guidelines on switching to long-acting injectable risperidone (1), extrapyramidal symptoms still developed in our patients within 24 hours of the depot injections. These symptoms maybe attributed to the initial release of risperidone in the bloodstream.

After a single intramuscular injection of risperidone, there is a small initial release of drug (<1% of the dose), followed by a lag time of 3 weeks when risperidone is not released. After the intramuscular injection, the main release of the drug starts at week 3 and is maintained from 4 to 6 weeks. The release of the drug begins to decrease at week 7 (2).

To limit the risk of developing extrapyramidal symptoms around the time of the injection, it may occasionally be necessary to reduce or omit the dose of the oral antipsychotic in the days after the injection. Attention should be paid to the half-life of any other depot drug given in the period before the initiation of injectable risperidone.

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Seizures and Prolonged QTc With Atomoxetine Overdose

To the Editor: Atomoxetine is a new norepinephrine reuptake inhibitor indicated for attention deficit hyperactivity disorder (ADHD). We present a case of atomoxetine overdose with consequent seizures and prolongation of the QTc interval.

Adam was a 15-year-old Caucasian adolescent who weighed 54 kg and had a history of major depression and ADHD. He was brought to the emergency department after an intentional overdose of atomoxetine. There was no past history of seizures, head injury, medical illness, or substance abuse. His medications included 150 mg b.i.d. of sustained-release buproprion, 0.25 mg b.i.d. of risperidone, 0.25 mg of alprazolam as needed, and 80 mg/day of atomoxetine. He had been taking bupropion for the past 1½ years and risperidone for the past 7 months. Two months before we saw him, he was switched from amphetamine to atomoxetine, 60 mg/day. Two weeks before we saw him, his atomoxetine dose was increased to 80 mg/day, and his bupropion dose was decreased to 150 mg b.i.d. because of continued ADHD symptoms. Soon after this change, however, he relapsed into severe depression.

Adam ingested 1200 mg (22 mg/kg) of atomoxetine about 1½ hours before coming to the emergency department. Pill counts confirmed that this was the only drug involved. He was treated with intravenous fluids and charcoal. About 3 hours after ingestion, he had a witnessed generalized seizure with postictal confusion that spontaneously resolved. He had a second generalized seizure 2 hours later that was treated with two doses of intravenous diazepam, 5 mg, and a loading dose of phenytoin. He was transferred to the medical intensive care unit for observation. The Poison Control Center had no specific recommendations.

Adam complained of anxiety, tremulousness, and dry mouth during the first few hours. A physical examination showed an alert, oriented, anxious, and afebrile patient with a pulse in the 110s and a stable systolic blood pressure in the low 100s, with equal and reactive pupils and fine motor tremors. A neurological examination produced nonfocal results. Routine blood tests produced normal results. The results of a urine toxicology screen and tests for alcohol, acetaminophen, and salicylate were negative. His QTc interval was 607 msec at 3 hours and 435 msec at 6 hours after ingestion. Adam was discharged 2 days later to an inpatient psychiatric facility.

We believe this to be the first published case of atomoxetine overdose. The drug has a half-life of 5 hours and is metabolized by the P450 2D6 enzyme (1). Coadministration with 2D6 inhibitors, such as paroxetine and fluoxetine, can increase serum atomoxetine levels three- to fourfold (2). Animal studies have found convulsive activity at doses of 12 mg/kg and higher (data on file, Eli Lilly, 2002). The higher serum level of atomoxetine, or its main metabolite, hydroxyatomoxetine, may have caused our patient's seizures and cardiac conduction delay. Bupropion may have contributed to the seizures (3). Since atomoxetine is not a controlled drug, there is likely increased accessibility for abuse and overdose. Further research is needed to explore the risks of seizure and arrhythmia with atomoxetine and to develop guidelines for the management of overdose and toxicity. Until more data are available, we advise caution when using atomoxetine in individuals at risk for seizure or receiving 2D6 inhibitors.

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Tardive Dyskinesia in an Autistic Patient Treated With Risperidone

To the Editor: Several open-label trials and case reports have suggested the usefulness of risperidone in treating maladaptive behaviors associated with autism (1–3). More recently, a double-blind, placebo-controlled study (4) has shown that risperidone reduces symptoms such as irritability, stereotypy, hyperactivity, aggression, and self-injurious behavior in children with autism. However, these reports also acknowledged that the relatively brief periods of treatment have precluded conclusions about the safety of risperidone with respect to tardive dyskinesia in children with autism. The following is a case report of an adolescent boy with autism who developed tardive dyskinesia while being treated with risperidone.

Alex was a 14-year-old boy who was brought to the Stanford University Pervasive Developmental Disorders Clinic for increasingly aggressive and disruptive behavior. He had been diagnosed with autism at an early age. The diagnosis was confirmed with DSM-IV criteria. Although the aggres-

sion began earlier in childhood, he was becoming progressively more dangerous in his community because of his increasing size and the increasingly frequent and indiscriminate nature of his assaultive behavior. Previously, numerous medications were prescribed for Alex, including stimulants, selective serotonin reuptake inhibitors, tricyclic antidepressants, buspirone, and secretin. Of note, Alex had never received any antipsychotic medications.

Risperidone was begun at 0.5 mg/day in our clinic and was increased gradually because of ongoing episodes of aggression and impulsivity. Alex's dose eventually reached 3 mg/day after 16 months of treatment. Shortly thereafter, Alex's behavior improved dramatically, with decreased aggression, less hyperactivity, improved language functioning, and increased sociability.

By the 23rd month of treatment, Alex began to develop a "jerking" of his trunk and abdomen. He and his mother reported that he was moving and writhing his shoulders and trunk throughout the day. Upon examination, Alex had periodic choreic movements of his shoulders and trunk. No oral, lingual, or buccal movements were seen or reported. A neurological examination revealed no other abnormalities. Trials of anticholinergic agents and vitamin E proved to be of little to no benefit. When risperidone was reduced to 2 mg/day, Alex's behavior deteriorated dramatically, so his dose was returned to 3 mg/day. Subsequently, Alex also experienced dyskinetic movements in the oculomotor muscles.

After numerous discussions with Alex and his parents about the risks and benefits of risperidone, Alex continues to take risperidone at 3 mg/day, along with benztropine, 2 mg b.i.d., and a vitamin E supplement. He continues to benefit behaviorally from the drug regimen.

This report presents the emergence of tardive dyskinesia secondary to risperidone in an individual with autism who had previously been naive to antipsychotics. This case demonstrates the effectiveness of risperidone in treating the disruptive behaviors of autism. The use of atypical antipsychotics to ameliorate the maladaptive behaviors associated with autism is likely to increase, given the absence of treatments that robustly address its core symptoms. The case points to the need for a careful discussion of the potential risks and benefits of risperidone, the identification of specific target symptoms, and education regarding the time course of treatment. The risk of tardive dyskinesia should be discussed explicitly. There should also be thorough discussions about pharmacological and nonpharmacological interventions that may need to be exhausted before considering the use of antipsychotic medications.

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Can Interpersonal Loss Precipitate Panic Disorder?

TO THE EDITOR: A central aspect of the DSM-IV diagnosis of panic disorder is that the symptoms appear to come "out of the blue." Nonetheless, there is a substantial literature documenting psychosocial stressors precipitating panic disorder (for example, references 1 and 2) and, specifically, anxiety disorders in bereavement (3). No investigator to date, to our knowledge, has examined the frequency of events involving interpersonal loss (through death or relationship disruption) that immediately preceded the onset of panic disorder.

We examined the frequency of interpersonal loss events immediately preceding the onset of panic disorder (within 6 weeks) in two groups of patients with panic disorder, both of whom participated in the evaluation of efficacy of panic-focused psychodynamic psychotherapy at Weill Medical College of Cornell University (4).

We examined the onset of panic in 51 patients, 21 of whom had participated in an open trial of panic-focused psychodynamic psychotherapy (5) and 30 of whom had been treated in an ongoing randomized, controlled clinical trial, as rated on the Anxiety Disorders Interview Schedule for DSM-IV: Lifetime Version (6). All patients met DSM-IV criteria for panic disorder with or without agoraphobia.

Twenty-four (47%) of our patients experienced an onset of panic disorder within 6 weeks after a significant interpersonal loss. Without a control group, it is not clear whether a similar rate of interpersonal loss would be found for patients in other diagnostic groups.

Panic disorder has heretofore not been conceptualized in the psychiatric literature as an outcome of loss or a form of complicated bereavement. It will be important to determine whether other groups of panic patients experience panic onset after loss with the same high frequency. It remains to be determined whether the history of interpersonal loss in panic onset may function to moderate the outcome of specific treatment interventions (7).

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