Letters to the Editor

Reversal of Antipsychotic-Induced Hyperprolactinemia, Weight Gain, and Dyslipidemia by Aripiprazole: A Case Report

Sir: The association between antipsychotics and increased risks of hyperprolactinemia,[1] weight gain,[2] and dyslipidemia[3] is well recognized. Recently, Wahl and Ostroff[4] reported a case of successful treatment of symptomatic hyperprolactinemia using aripiprazole. This report presents a case of reversed risperidone-induced hyperprolactinemia, weight gain, and dyslipidemia by aripiprazole before discontinuation of risperidone.

Case report. Ms. A, a 39-year-old woman, had a history of paranoid schizophrenia (DSM-IV criteria). She was administered risperidone, 4 mg/day, for about 9 years. She had very good adherence to her medical regimen and partial response to risperidone. However, the patient suffered gradual weight gain (weight, from 48 kg to 62 kg; height, 153 cm), persistent oligomenorrhea, and breast swelling. Serum prolactin was 141.4 ng/mL (normal range, 2.8–29.2 ng/mL) in 1998, and had not since returned to normal range during follow-up examinations.

In December 2003, Ms. A was diagnosed with a teratoma over the right ovary and soon underwent laparotomy enucleation of the tumor. In June 2005, she had normal or borderline blood levels of glucose, total cholesterol (TC), and triglycerides, but had an elevated level (164 mg/dL; normal range: < 130 mg/dL) of low-density lipoprotein cholesterol (LDL-C) and a low level (27 mg/dL; normal range: > 40 mg/dL) of high-density lipoprotein cholesterol (HDL-C). The TC/HDL-C ratio and LDL-C/HDL-C ratio were 7.6 (normal range: < 4.4) and 6.0 (normal range: < 3.2), respectively.

In June 2005, Ms. A was diagnosed with exacerbated psychotic symptoms, including auditory hallucinations, delusion of persecution, and delusion of being controlled, in the absence of increased stress or discontinuation of medication. She was referred to our unit after an acute exacerbation of psychosis and persistent adverse effects from risperidone.

A cross-switch from risperidone to aripiprazole was proposed. Aripiprazole was titrated from 10 to 20 mg/day during 5 weeks. Psychotic symptoms abated in the sixth week after aripiprazole was added, but were not fully resolved. After 9 weeks, her risperidone dosage was reduced from 4 mg/day to 3 mg/day during the next 2 weeks; her psychotic symptoms flared up again during this 2-week period. At week 11, her risperidone dosage was returned to 4 mg/day. She was then maintained on risperidone, 4 mg/day, and aripiprazole, 20 mg/day, until a successful switch to aripiprazole monotherapy was made at week 20. The serum prolactin level decreased from 130 ng/mL at the baseline to 13.1 ng/mL at week 6. Her breast swelling and oligomenorrhea resolved, and her body weight decreased from 62 kg at the baseline to 57 kg at week 6 and to 51.5 kg at week 16. The HDL-C level, TC/HDL-C ratio, and LDL-C/HDL-C ratio were 40 mg/dL, 5.4, and 4.1, respectively, at week 16.

Aripiprazole is associated with lower risk for weight gain and hyperprolactinemia compared with other atypical antipsychotics.[5] There are case reports of resolution of antipsychotic-induced hyperprolactinemia[6] and hyperlipidemia[7] after switching to aripiprazole. The case we describe here had resolution of hyperprolactinemia before any reduction of risperidone dose. Aripiprazole has a high affinity for the dopamine D_2 receptor and roughly 30% of intrinsic activity at postsynaptic receptors.[8] This partial agonist property of aripiprazole can most likely explain the mechanism through which it reverses adverse effects caused by other antipsychotics. Aripiprazole may block risperidone's binding on dopamine D_2 receptor and serotonin-2A receptors. Therefore, it may be unnecessary to use aripiprazole and risperidone concomitantly for treating psychotic symptoms. However, switches between antipsychotics sometimes take several weeks or several months and are not always successful. A controlled trial is required prior to determining whether aripiprazole is beneficial for treating antipsychotic-induced hyperprolactinemia, weight gain, or dyslipidemia.

Drs. Lin and Chen report no financial affiliation relevant to the subject of this letter.

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Sedative Effects of Low-Dose Risperidone in GAD Patients and Risk of Drug Interactions

Sir: Based on their results, Brawman-Mintzer et al.[1] suggest that adjunctive risperidone at low doses may represent a useful tool in the management of symptomatic generalized anxiety disorder (GAD) patients. They found statistically significant improvements in core anxiety symptoms as demonstrated by greater reduction in Hamilton Rating Scale for Anxiety (HAM-A) total scores (p = .034) and HAM-A psychic anxiety factor scores (p = .047) compared with placebo. The authors also conclude that between-group differences in reported adverse events were not clinically significant.

However, scrutinizing their data[1] reveals a statistically significant between-group difference for somnolence: more

risperidone-treated patients reported somnolence (9 of 19) than placebo-treated patients (3 of 20; Fisher exact test, 2-tailed, p = .047). This statistical difference can arguably be of clinical relevance, since risperidone-induced calming effects may be in fact attributed to sedation rather than to specific anxiolytic effects.

Somnolence in the risperidone group can be partially explained by drug-drug interactions. Risperidone is metabolized via cytochrome P450 (CYP) enzyme 2D6, and coadministration of the CYP2D6 inhibitors fluoxetine (N = 2),[2] bupropion (N = 1),[3] and sertraline (N = 1)[4] could have increased plasma levels of risperidone. After 4 weeks of concomitant risperidone and fluoxetine treatment, Spina et al.[2] found that the levels of active moiety (sum of the concentrations of risperidone and 9-OH-risperidone) increased by 75% (range, 9%–204%). Higher plasma levels of risperidone can result in subsequent dose-related side effects, e.g., a reported combination of risperidone 0.5 mg and fluoxetine produced gynecomastia.[5]

Specific anxiolytic effects of risperidone in GAD patients should be further studied to differentiate them from nonspecific sedating effects, but adjunctive risperidone should be used only in patients treated with anxiolytics that do not have CYP2D6 inhibition (alprazolam, buspirone, clonazepam, diazepam) or that are weak inhibitors of CYP2D6 (citalopram, venlafaxine).

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Dr. Brawman-Mintzer and Colleagues Reply

Sir: We appreciate the comments of Drs. Kopecek, Mohr, and Novak in response to our report suggesting that risperidone at low doses may represent a useful tool in the management of symptomatic GAD patients.[1] Two issues are brought to our attention that were only marginally addressed in the original report.

First, the possibility is raised that risperidone could have contributed to the somnolence experienced by some patients. In this regard, we noted previously that between-group differences in reported adverse events were not clinically significant. This lack of clinical difference occurred despite the apparent minimal statistical difference reported by Kopecek et al. in reanalyzing our data. Several facts about this pilot study should be noted. For example, all of the patients who were enrolled in the trial were not responding adequately to their existing anxiolytic therapy, despite drug dosages received by many patients in the range of recommended therapeutic doses. Thus, the addition of any agent to an existing treatment needs to be considered in light of the possible benefits and risks. All of the previously existing anxiolytic treatments in our patients are capable of causing somnolence, and it would not come as a surprise to us if some additive effect occurred with the addition of risperidone, even at low doses. However, the majority of patients in the risperidone group (10/19) did not experience somnolence. Had this been a practice setting rather than a controlled clinical trial, the addition of risperidone, when indicated, might have been accompanied by a reduction in the dosage of the preexisting anxiolytic. However, in this trial of patients showing inadequate prior treatment response, no such adjustment of dosage was allowed in order to maintain the integrity of the trial design.

Additionally, as many patients develop an apparent tolerance to the sedating effects of otherwise effective anxiolytic treatments, we cannot discount the possibility that such a compensating effect would also occur in those patients experiencing somnolence, had they been able to continue risperidone treatment past study endpoint. Nevertheless, the comment by Kopecek et al. is an appropriate reminder that close clinical observation and discussion of potential adverse events from all treatments is a desirable approach to optimize anxiolytic treatment in GAD patients.

Second, regarding the issue of drug interactions that Kopecek et al. raise, we doubt that this possibility had any substantial effect on the outcome of the trial. We also must disagree with the conclusion that adjunctive risperidone should be used only in patients treated with anxiolytics devoid of any CYP2D6 inhibition. In our study, only 7 of the 19 patients receiving risperidone were treated with a previous anxiolytic that has any degree of CYP2D6 inhibition (4 patients with sertraline, 2 with fluoxetine, 1 with bupropion). We would also discount any meaningful interaction in patients receiving sertraline, as that drug has been previously demonstrated not to be associated with clinically significant changes in plasma risperidone concentration.[2] Thus, only 3 patients might have experienced a pharmacokinetic interaction, making it unlikely that such a drug interaction would have significantly altered the outcome of the trial.

It should also be noted that the order in which drug treatment occurs is important in assessing the significance of a drug interaction between risperidone and a CYP2D6 inhibitor. In all 3 patients, the therapy with CYP2D6 inhibitory properties existed prior to initiation of risperidone. Thus, any effect on risperidone metabolism should have occurred with the first dose of risperidone. The most pronounced effect that could have occurred would be a higher risperidone concentration with the 0.5-mg dose than would have occurred without the existing anxiolytic treatment. As the study design allowed an upward titration of dosage from 0.5 to 1.0 to 1.5 mg of risperidone, presumably if this situation occurred in clinical practice, any beneficial effect of risperidone in GAD would occur at a low dose. Since the mean dose at the end of the trial was only 1.1 mg, we doubt that this potential interaction could have played any role in the outcome of the study.

Thus, we feel it is appropriate, on the basis of the results of this pilot, double-blind study, to further explore the prospective effects of risperidone in GAD. We thank Kopecek et al. for reminding us of the need for vigilance in evaluating the effects of combined drugs on patient response when drug interactions may occur.

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A Case of Probable Bipolar VI Disorder?

Sir: The presence of mania is more prominent in dementia than in other neuropsychiatric disorders or chronic illnesses.[1,2] The profile of delirium and delusions in the course of dementia was reported to be different from that seen in schizophrenia.[3] Debates on the definition of "psychosis related to Alzheimer's disease" as a new phenomenon are ongoing, and Akiskal and colleagues[4] recently proposed the use of the term *bipolar VI disorder* for patients who present with cognitive impairment and mood symptoms.

We present a case that is consistent with this new concept of bipolar VI disorder. The initial presentation of the case was with symptoms of late-onset mood disorder, followed later by dementia.

Case report. Ms. A, a 59-year-old woman, presented for the first time following a suicide attempt shortly after a surgical intervention for knee prosthesis. She had complaints of anxiety, anhedonia, loss of interest, fatigue, decreased ability to concentrate, psychomotor retardation, and sleeplessness. She expressed that she had lost hope for recovery despite the fact that her knee surgery had been successful. She was hospitalized with the diagnosis of major depressive episode (DSM-IV), and full remission was achieved in 1 month with venlafaxine 150 mg and clonazepam 2 mg daily. The patient discontinued the medication following a treatment period of 9 months.

Approximately 3 months after discontinuing her medication, Ms. A returned with symptoms of mania such as inflated self-esteem, socially and sexually inappropriate behavior (opening the curtains and walking around naked at home), distractibility, increased expenditure, increase in goal-directed activity (selling her house to cover her debts), grandiose and persecutory delusions, and auditory and visual hallucinations. Her treatment started with risperidone 8 mg, diazepam 6 mg, and biperiden 2 mg daily, but was unsuccessful after a period of 4 weeks. The medications were then replaced by amisulpride 400 mg and chlorpromazine 200 mg daily and a 25-mg injection of fluphenazine decanoate. She responded partially in 2 weeks, but was readmitted because of noncompliance and ongoing symptoms such as distractibility, irritability, agitation, and irregular sleep.

Her history was reviewed in detail to rule out an earlier episode of mania or depression. Both Ms. A and her relatives confirmed that she had no psychiatric symptoms before the age of 59 years. Her family history was negative for any psychiatric disorder except for a sister who had a major depressive episode at the age of 53 years and was successfully treated with a selective serotonin reuptake inhibitor.

Physical examination, complete blood count, thyroid functions, and vitamin B_{12} and folic acid levels were within normal limits. Neurologic examination showed no abnormalities except for moderate signs of parkinsonism (static tremor, cogwheel rigidity, bradykinesia, and postural instability), which were considered to be drug induced. She had a total score of 32 on the Unified Parkinson's Disease Rating Scale–Motor Examination (UPDRS-ME).[5] Cranial magnetic resonance imaging (MRI) revealed cerebral and cerebellar atrophy and multiple ischemic gliotic lesions located bilaterally in the periventricular subcortical white matter, the basal ganglia, and the pons.

Her diagnosis was changed to bipolar disorder, manic episode, severe with psychotic features, and neuroleptic-induced parkinsonism (all DSM-IV). Valproate 1000 mg, clonazepam 1 mg, and biperiden 4 mg daily were started. Her manic symptoms partially improved in the following few days; however, irritability and episodes of agitation continued. She also developed cognitive signs and symptoms, which mainly consisted of deficits in attention, concentration, and short-term memory. Her score on the Mini-Mental State Examination (MMSE),[6] conducted within a few days after the start of the new treatment regimen, was 15. Cognitive findings showed no fluctuation; therefore, the clinical picture was not considered to be compatible with delirium. Rather, the clinical picture was one that started with mood symptoms and slowly progressed to cognitive deficits. The severity of parkinsonism had also increased at this timepoint; her UPDRS-ME score was 72, and she did not respond to biperiden 8 mg daily. Levodopa at a dose of 250 mg daily was started, and her parkinsonism improved considerably within 3 days. However, since psychotic symptoms reemerged within a few days after the initiation of levodopa treatment, treatment was changed to clozapine 200 mg, biperiden 1 mg, and clonazepam 0.5 mg daily. The latter 2 were shortly tapered off because of their potential for adverse cognitive effects. At this time, Ms. A was discharged, showing partial improvement in mood and psychotic symptoms and having a UPDRS-ME score of 22. Two weeks after discharge, there was no change in cranial MRI findings, her UPDRS-ME score had decreased to 17, and her MMSE score had increased to 27. The partial improvement in cognitive deficits suggested that these deficits might have been at least partially caused by her medication.

At monthly follow-up visits, her mood symptoms never achieved full remission, and she continued to have thoughts of hopelessness, difficulty sleeping, and decreased psychomotor activity. Approximately 1 year later, lamotrigine and lithium were added to her treatment and were gradually increased to daily doses of 150 mg and 600 mg/day, respectively. Symptoms of hopelessness and anhedonia partially improved in the months

that followed. Her cognitive dysfunction, on the other hand, showed progression, and bradykinesia did not improve completely. Impairment of short-term memory and deficits in judgment and executive functions were severe enough to render the patient unable to take care of herself. Taken together with the findings on the cranial MRI, her symptoms fulfilled the DSM-IV diagnostic criteria for vascular dementia.

This case met the diagnostic criteria for both late-onset bipolar disorder and vascular dementia. However, the late onset of mood episodes, their inadequate response to mood stabilizers, and the accompanying dementia were all atypical features. Cognitive dysfunction was observed at a time when it was impossible to rule out medication side effects as a cause; however, the rapid progression as well as the ongoing signs of parkinsonism suggested that cerebral ischemia was a better explanation.[2]

With the late onset of mood symptoms that never fully responded to antipsychotics or mood stabilizers, progression to irritability, attention and concentration problems, and a subsequent onset of full-blown dementia, this case might be considered as a probable bipolar VI disorder. This clinical course is compatible with what was described by Akiskal and others[4]: mood symptoms were not present until 59 years of age; premorbid personality was described as strong and adaptive; and irritability, agitation, and sleep disturbance were added to problems in memory and concentration after a while (the patient and her close relatives were in search of medical aid because of problems in memory and behavioral changes). Also, after an improvement period of a short time, features of mood disorder increased after antidepressant treatment. In general, she was unable to tolerate valproate, which might have been a good option for treatment. Her response to lithium was satisfactory. Although mood episodes were not completely treated and prevented, she has not been suicidal again, the number and severity of depressive episodes clearly decreased, and she has never had another episode of mania.

As noted in a review by Strakowski and colleagues,[7] the types of brain structure changes observed in brain imaging studies of bipolar patients vary greatly and are not, in fact, unique to bipolar disorder. Ventricular widening, which was observed in our patient, was a common finding; structural impairments in basal ganglia and striatal structures and hyperintense regions at white matter are also reported as other common findings.[7] Similar findings have been reported in patients with dementia.[8] Akiskal et al.[4] considered that bipolar spectrum disorder and Alzheimer's disease might have common features in their pathogeneses.

The diagnosis of bipolar VI disorder definitely needs to be validated with prospective studies; however, retrospective studies and case reports may be helpful until prospective studies provide evidence for or against establishing this new phenomenon as a valid category.

The authors report no financial affiliation relevant to the subject of this letter.

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Initial Dosing Strategies for Long-Acting Injectable Risperidone

Sir: What are the most effective initial dosing strategies when starting long-acting injectable risperidone? Vials are available in 3 doses: 25, 37.5, and 50 mg. As clinicians continue to gain experience in prescribing risperidone in this new injectable form, a review of initial dosing strategies when starting a patient on long-acting injectable risperidone is needed.

Method. We performed a retrospective uncontrolled review of outpatients with serious mental illness treated with long-acting injectable risperidone at the Washoe Community Mental Health Clinic (Reno, Nev.), noting the starting doses and following the patients' doses over a cross-sectional time period of 1 year (between July 2004 and June 2005) during the course of their illnesses. The total number of individual patients was 40. The total number of injections given was 438.

The patients suffered from schizophrenia (DSM-IV). Risperidone was titrated to treat positive psychotic symptoms on the basis of clinical judgment, so the severity of the symptoms necessary to decide that the dose was not effective could be different for each patient at different timepoints during treatment. Polypharmacy and combination pharmacotherapy were common among the treating physicians, so this was not a controlled study and no uniform criteria were in place for patient management. The frequency of administration of each dose was every 2 weeks. Records of the injections were obtained from the pharmacy.

Patients who received 3 or fewer injections over the 12-month period were excluded from further data analysis. The groups receiving the higher doses progressed from lower initial doses and remained in treatment long enough to reach the higher levels. No patients were started on higher doses.

Results. Twenty-two patients were included in the 25-mg group. The mean duration of treatment at this dose was 14 weeks. This group had a dropout rate of 32% (7 of 22). Of the remaining patients, 33% (5 of 15) were maintained on this same dose and did not require a dose increase. Sixty-seven percent of the patients (10 of 15) on the 25-mg dose did require a dose increase. Of those 10 patients on the 25-mg dose who required a dose increase, 90% (9 of 10) eventually required the 50-mg dose.

Eleven patients were included in the 37.5-mg group. The mean time subjects spent at this dose was 18 weeks. The dropout rate in this group was 45% (5 of 11). Of the remaining patients, 50% (3 of 6) required a higher dose.

Seven patients were included in the 50-mg group. The mean time spent on this dose was 35 weeks. The dropout rate in this group was 14% (1 of 7), and none of the remaining patients required any dose adjustments during the 1-year period.

We conclude that long-acting injectable risperidone should not be started at a dose higher than 25 mg. However, because a majority of patients do not respond to the 25-mg or the 37.5-mg dose and ultimately require the 50-mg dose, it may be prudent to consider increasing after 2 doses of 25 mg every 2 weeks directly to 50 mg every 2 weeks for patients who fail to respond to the lower doses. This notion supports the clinical trials data, which emphasized a significant improvement in positive symptoms with 50 mg versus 25 mg.[1,2] Vacillating between 25-mg and 37.5-mg doses for several months is not cost-efficient and may appear to be ineffective for some schizophrenic patients.

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Aripiprazole Augmentation of Venlafaxine in the Treatment of Psychogenic Excoriation

Sir: Psychogenic excoriation, or pathologic skin picking, is a well-recognized syndrome characterized by excessive scratching or picking of normal skin or skin with minor irregularities.[1] Case studies, open trials, and small double-blind studies report efficacy with selective serotonin reuptake inhibitors.[1] We describe a female patient whose psychogenic excoriation was unresponsive to a serotonin-norepinephrine reuptake inhibitor, but improved markedly when aripiprazole was added.

Case report. Ms. A, a 50-year-old woman, was diagnosed with "depression" and "anxiety" by a primary care physician in 2001 and was formally diagnosed with comorbid major depressive disorder and generalized anxiety disorder (DSM-IV) when she first presented to our practice the following year. She had a 20-year history of psychogenic excoriation with associated alopecia. Depressive and anxiety symptoms were effectively treated by venlafaxine, which was started at 150 mg/day 2 months before she presented to our practice and which we raised to 375 mg/day during the 3 months after her presentation, but minimal effects on her itching and excoriation resulted.

Her arms, legs, and face had multiple sites of chronic excoriation due to itching and burning sensations, and her scalp displayed 2 patches (2 to 3 cm) of alopecia. Her symptoms had improved approximately 50% when risperidone, 1 mg daily, was added to venlafaxine 2 years after her initial presentation to our practice, but risperidone therapy was discontinued when she experienced edema in her legs and arms. She did not intentionally pull out her hair, but alopecia resulted from her picking at her scalp. She had no sustained belief that insects were present and had no symptoms of obsessive-compulsive disorder (OCD) or body dysmorphic disorder. Her dermatologist diagnosed psychogenic dermatitis and recommended fluoxetine, but since her dermatitis had failed to improve with an earlier (2001) trial of paroxetine, the decision was made (2 months after the risperidone trial had been started) to augment venlafaxine with aripiprazole, 10 mg daily, rather than to change antidepressant medications.

Six weeks later, Ms. A presented with healed excoriations on her arms and face. No new lesions were evident, and the alopecia was resolving. The benefit was sustained at 6 months, and the only side effect experienced was a 16-lb weight gain.

Psychogenic excoriation, an impulse-control disorder, has been treated successfully with fluoxetine, fluvoxamine, and paroxetine.[1] Effective treatment of this patient's anxiety and depression was obtained with venlafaxine, so aripiprazole augmentation was employed. Case reports exist for olanzapine augmentation of fluoxetine for both psychogenic excoriation[2] and trichotillomania.[3] For this patient, risperidone and then aripiprazole were chosen owing to concerns about possible weight gain associated with olanzapine. One open-label trial reported aripiprazole to be effective as monotherapy for OCD.[4] Aripiprazole, a partial agonist at serotonin-1A (5-HT_{1A}) receptors and dopamine-2 receptors and a blocker of 5-HT_{2A} receptors, may mechanistically fit with hypotheses regarding the neurochemical pathology of OCD. This case suggests a possible role for aripiprazole augmentation of venlafaxine and perhaps of other serotonergic medications, such as the selective serotonin reuptake inhibitors, in the treatment of psychogenic excoriation.

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