Resolution of Late-Onset Hypomania After Repair of Carotid Artery Stenosis: A Case of Vascular Hypomania

Sir: Ischemia from cerebrovascular disease may be etiologically important in a subtype of geriatric depression called *vascular depression*.[1] It is less clear if a similar subtype of vascular mania exists. However, patients with late-onset mania have more vascular risk factors than those with early-onset, supporting the idea of a secondary mania related to cerebrovascular disease.[2]

Elderly patients with mania have also been found to have more severe frontal lobe magnetic resonance imaging (MRI) signal hyperintensities than elderly control patients, suggesting a relationship between frontal lobe lesions and mania.[3] Further research has described the relationship between right-sided lesions and secondary mania.[4] We describe the resolution of hypomanic symptoms after bilateral carotid endarterectomy in a patient with long-standing unipolar depression who developed late-onset hypomania with MRI white matter hyperintensities.

Case report. Mr. A, a 67-year-old left-handed man with long-standing diabetes mellitus and coronary artery disease, was diagnosed with unipolar recurrent depression 40 years ago. Three years ago, he developed decreased sleep, increased energy, racing thoughts, and prominent irritability while taking his long-standing maintenance antidepressant, escitalopram 20 mg q.d. These symptoms responded only partially to the addition of lamotrigine, aripiprazole, and daily clonazepam and the eventual discontinuation of escitalopram. His diagnosis was subsequently changed to DSM-IV bipolar II disorder.

Two separate attempts to taper off both the aripiprazole and the clonazepam failed when the patient experienced worsening insomnia and extreme irritability. The patient remained stable, but with subsyndromal symptoms, on this medication regimen for approximately 2 years. He then underwent a right carotid endarterectomy for critical stenosis of the right internal carotid artery followed 3 months later by a left carotid endarterectomy for occlusion of the cervical segment of the internal carotid artery, both discovered when he developed episodic aphasia. Prior to surgery, he had an MRI with contrast that revealed small foci of white matter hyperintensity in the right periventricular subependymal region, in the right superior frontal gyrus, and in the left cingulate gyrus. There were no infarcts observed. Within 3 weeks after his first surgery, he reported a dramatic improvement in his mood, and 1 month after his second surgery, his symptoms completely remitted, and he felt himself again. Aripiprazole and clonazepam were discontinued, and at his 4-month follow-up, he remains well, taking lamotrigine, without any irritability or difficulties sleeping.

The temporal relationship between the resolution of this patient's symptoms and his surgeries suggests that his irritability and insomnia, the cornerstones of his bipolar II diagnosis, were at least in part mediated by decreased cerebral blood flow due to carotid stenosis. When the blood flow was restored, his symptoms abated. The MRI findings are consistent with previous research that demonstrated a relationship between right-sided lesions and secondary mania[4] as well as a correlation between bipolar disorder and hyperintensities in the subependymal region, deep white matter, and subcortical gray nuclei.[5] In addition, this case demonstrates that treating the complications of vascular disease, in this case carotid stenosis, can have a striking impact on psychiatric symptoms. Furthermore, in this case, treatment of the effects of vascular disease allowed the discontinuation of a psychiatric medication, aripiprazole, a member of a class of medications that has been linked to adverse vascular events and glucose intolerance.[7,8]

A syndrome shift in late life from unipolar depression to bipolar disorder should raise a red flag for secondary mania. Physicians should thoroughly evaluate such patients for diseases that affect the cerebrovasculature, including carotid stenosis. Successful treatment of carotid stenosis may not only avoid medical morbidity[6] but improve psychiatric symptoms and spare patients from potentially unneeded medication.

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Augmentation of Clozapine Treatment With Aripiprazole

Sir: We read with great interest the recent (April 2006) report by Clarke et al.[1] As noted in their report, our group[2] found similar improvement in negative symptoms when clozapine was added to the regimen of 3 inpatients admitted for acute psychoses refractory to aripiprazole monotherapy. As our patients were all in an acute hospital setting when the combination was used, we were pleased to read that this regimen may have similar effects when used with patients in the outpatient setting as well.

We would like to make a clarification, however. Clarke et al. refer to the cases in our report as cases of clozapine augmentation of aripiprazole. Although, in our patients, clozapine was

initiated while the patients were still on aripiprazole treatment, the notable finding was not only the improvement in negative symptoms, but also that all 3 patients with long-standing psychotic illnesses significantly improved with lower-than-expected doses of clozapine. Clozapine doses for our patients ranged from 150 to 200 mg/day. Although clozapine was initially supposed to be the sole antipsychotic for our patients, aripiprazole was maintained due to the observed significant improvement in both positive and negative symptoms at relatively low doses of clozapine. Therefore, we hypothesized that aripiprazole was more likely the augmenting agent.

Dr. Clarke was shown this letter and declined to comment.
Drs. Lim and Bowers report no financial or other relationship relevant to the subject of this letter.

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What Do We Know About Insulin Resistance and Glucose Metabolism in Patients With Schizophrenia Treated With Antipsychotics?

Sir: In their recent article on glucose metabolism in schizophrenic patients during treatment with olanzapine or quetiapine, Henderson et al.[1] have raised some important issues.

We wish to begin by complimenting the authors on their efforts to clarify a complex issue that attracts much attention in the literature. Their article is important for hypothesis generation in the area of understanding insulin resistance issues among patients treated with antipsychotics. However, their work must be interpreted within the limitations of the study. It is cross-sectional, which allows for selection bias and does not consider previous treatment or illness (both metabolic and psychiatric) history. The sample size is small, and the authors make many statistical comparisons without adjusting for multiple comparisons. Generalizability is also limited due to the exclusion of obese patients.

There have been several studies of insulin resistance in patients treated with antipsychotics; however, each has its limitations.[1–17] Taken together, these data still do not answer the question, as these studies were cross-sectional,[1–4,7,9–11,13,14] were limited by small sample size,[1,4–6,8,10,15,17] included differing populations,[17] utilized nonstandard techniques for assessing insulin resistance,[13] measured only surrogates of insulin sensitivity,[12] and had baseline differences in the treatment groups that may have biased the results.[7] It should also be considered that insulin resistance is a parameter that has an extremely wide variation of normal values—6-fold across normal healthy volunteers.[18] Eli Lilly is currently undertaking a study (see www.clinicaltrials.gov) that seeks to provide information on the issue of insulin resistance in patients treated with atypical antipsychotics and addresses several of these limitations.

Metabolic adverse events occurring during treatment with antipsychotics require careful diligence in management just as when they occur in other patients. Dietary changes or drugs such as statins may be required in some patients. Studies suggest that weight can be managed in some patients who continue long term with weight education programs,[19–27] but this is also far from easy. More research is needed to address this important clinical issue, especially because recent clinical studies suggest that patients more frequently discontinue their medications primarily due to lack of efficacy than due to lack of tolerability.[28,29] More and better risk management information is needed to support patient treatment options that offer sustained efficacy, functional improvements, and optimal prognoses.

Drs. Karagianis, Hoffmann, and Stauffer are employees of and stock shareholders in Eli Lilly. Dr. Treuer is an employee of Eli Lilly.

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Sir: Henderson et al.[1] raise the issue of glucose metabolism in olanzapine- and quetiapine-treated patients. The strengths of the study are the great work undertaken in laboratory and anthropometric measures, the use of a control group, and the inclusion of variables such as family history of diabetes, nicotine habit, and concomitant treatment with selective serotonin reuptake inhibitors. However, it is a pity the sample consisted of only 7 patients receiving quetiapine and 8 receiving olanzapine and that the duration of medication in the olanzapine group was 10 months longer than in the quetiapine group (the difference was statistically nonsignificant probably due to the large standard deviation).

The overwhelming information that has come up during the last decade about antipsychotic-induced weight gain, diabetes mellitus, insulin resistance, and metabolic syndrome has widely changed the clinical management of our patients with schizophrenia with regard to the screening and monitoring of the metabolic side effects of the antipsychotic treatment.[2]

But, do all antipsychotics induce these metabolic changes,[3] or is there a genetic protection or predisposition[4]? Several high-quality updated reviews have summarized the conflicting findings reported so far.[3,5–10] In agreement with the preceding letter by Karagianis et al., 2 of the most important factors to be considered are the characteristics of the patients included and the study design. Under the weakest study design, all antipsychotics seem to be associated with significantly higher odds of diabetes, which is not the case under strong study design.[3] The issue of whether first-episode untreated patients with schizophrenia do or do not show underlying metabolic abnormalities is still at debate,[11–13] and an increasing urge exists to dispose of data on larger populations of first-episode never-treated schizophrenia patients randomized to treatment. On the other hand, studies performed in long-treated patients usually lack information about prior treatment with antipsychotics, antidepressants, and mood stabilizers, with the cumulative effect of these treatments possibly being a confounder factor in the liability to antipsychotic metabolic syndrome. Open-label nonrandomized studies do not contemplate the bias of clinicians' having prescribed antipsychotics with a higher liability of metabolic syndrome to those patients with lower baseline weight. In this respect, a baseline body mass index lower than 25 kg/m^2 seems to be a predictor of antipsychotic-induced weight gain.[14]

As already stated by the authors, the need arises to replicate the present study in a larger sample of patients with schizophrenia, preferably in first-episode never-treated psychotic patients, with a follow-up of months or years and with exhaustive medication records.

Dr. Arranz has received grant/research support from AstraZeneca, Eli Lilly, Pfizer, and Janssen; has received honoraria from Eli Lilly and Janssen; and has participated in speakers/advisory boards for Janssen. Dr. San has received grant/research support and honoraria and has participated in speakers/advisory boards for AstraZeneca, Eli Lilly, Pfizer, Janssen, and Wyeth.

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Dr. Henderson Replies

Sir: I appreciate the comments by Karagianis et al. and Arranz and San on the issue of antipsychotic agents, insulin resistance, and glucose metabolism. The authors touch upon very important topics and limitations to our study, which were addressed in the Discussion section of the article.[1] Arranz and San correctly point out that the sample size of our study was small and that olanzapine-treated subjects received the drug for a longer period of time. With such a small sample size, it was difficult to match to length of treatment with the drug (though subjects were required to have taken the drug for at least 6 months).

I also agree that there has yet to be a definitive study on the mechanisms and pathways to insulin resistance and its associations with antipsychotic drugs. While most studies examining glucose metabolism related to antipsychotic drugs have limitations, collectively they point to a pattern of increased risk for insulin resistance, hyperinsulinemia, hyperlipidemia, obesity, and type 2 diabetes mellitus with some antipsychotic drugs and not others. More compelling clinical data suggest that switching patients from one drug to another may improve metabolic markers and reverse the type 2 diabetes mellitus.[2,3]

In our recent article,[1] we again found that nonobese olanzapine-treated subjects were insulin resistant and had reduced glucose utilization, which was consistent with a previous study using similar sensitive procedures to examine glucose metabolism (frequently sampled intravenous glucose tolerance test).[4] Karagianis et al. correctly point out that the sample size was small and the cross-sectional approach introduced a sample bias. While prospective studies are important to understand the effects of the antipsychotic agents, it is difficult to control for the impact of weight if the propensity for weight gain differs between drugs. In our study, olanzapine- and quetiapine-treated subjects with body mass index (BMI) below 30 kg/m^2 were matched with normal controls. Limiting the BMI was an attempt to control for the impact of weight gain and obesity. In a sense, this was the best case scenario. The selection bias was actually favorable toward not finding insulin resistance in the antipsychotic drugs, as nonobese subjects who were less likely to have gained weight were enrolled. Obesity would potentially increase insulin resistance in some patients, as is seen in the general population.

As was observed in the CATIE study, olanzapine-treated subjects exhibited the greatest weight gain, while also exhibiting the greatest increase in fasting glucose and triglycerides.[5] In fact, in the CATIE study, it appears that more patients discontinued olanzapine as a result of metabolic side effects compared to other drugs. Additionally, the CATIE trial highlights the high prevalence of metabolic syndrome and cardiovascular risks in patients with schizophrenia.[6–8] Additionally, I have been less impressed with data that suggest that it is the underweight or normal weight (BMI < 25 kg/m^2) that predicts antipsychotic-induced weight gain. While there very well may be a genetic predisposition to antipsychotic-induced weight gain, in my clinical experience, patients treated with certain antipsychotic agents can gain a substantial amount of weight regardless of their pretreatment BMI.

Current understanding of the pathway to type 2 diabetes mellitus is insulin resistance with declining β-cell functioning. The elevated rates of type 2 diabetes mellitus that have been observed in patients with schizophrenia, and in particular clozapine- and olanzapine-treated patients, also suggest that insulin resistance plays a major role. Resistance of fat, muscle, and liver to insulin is the central pathophysiologic event in the development of type 2 diabetes mellitus, and genetic and environmental factors play a major role in this process.[9] There is increasing evidence that the adipose tissue not only produces free fatty acids that contribute to insulin resistance, but also acts as a relevant endocrine organ producing mediators (adipokines) that can modulate insulin signaling.[9]

We look forward to the results of the study being conducted by Eli Lilly and hope that it provides clarity in this very complicated area. The overall goal is to understand the complex etiology of weight gain, insulin resistance, and diabetes mellitus related to antipsychotic drugs and to develop interventions to reverse or prevent such occurrences. Studying first episode, medication-free schizophrenia subjects may yield the best data. However, in light of a substantial body of literature, going forward, it may be more difficult to conduct such studies in which subjects are potentially randomized to a drug with a significant risk of weight gain, insulin resistance, and hyperlipidemia. The selection and maintenance treatment with an antipsychotic agent should be based on potential efficacy, short- and long-term safety, and tolerability. The development of approaches that prevent or eliminate the occurrences of potential life-shortening medical morbidities is critical in the care of the chronically mentally ill.

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Decreased Lipoprotein Lipase as a Risk Factor for Atypical Neuroleptic–Induced Hypertriglyceridemia

Sir: Neuroleptics often increase appetite. This increased appetite can lead to severe hypertriglyceridemia in patients with uncommon congenital lipoprotein lipase (LPL) deficiency. During neuroleptic therapy, attention should be paid to the potential for severe hypertriglyceridemia (> 1000 mg/dL) that increases the risk of atherosclerosis and can cause fatal acute pancreatitis.[1,2] We report a case of severe hypertriglyceridemia and decreased LPL during a switch from risperidone to olanzapine and propose that decreased LPL is a risk factor for neuroleptic-induced lipid metabolism disorders.

Case report. In February 2004, Mr. A, an 18-year-old schizophrenic (DSM-IV) Japanese man (height 178 cm, weight 60.7 kg), was admitted to our hospital because of hallucinations and delusions. Risperidone therapy was initiated and relieved his positive symptoms, but negative symptoms remained. Since the patient wished to change the drug, 10 mg/day of olanzapine was added to risperidone on the 26th hospital day to begin an attempted switch from risperidone to olanzapine. Because of increased appetite, the patient began eating carbohydrate- and fat-rich snacks (e.g., chips, instant noodles) 2 to 4 times daily between meals. Blood tests showed elevated serum levels of fasting triglycerides (1018 mg/dL; reference value, 20–160 mg/dL) on the 46th hospital day. His weight increased from 63.1 to 70.2 kg between the 28th and 47th hospital days.

Olanzapine therapy was terminated on the 47th hospital day. Diet therapy and exercise began with energy intake restriction (< 2300 kcal/day) and patient education about diet and exercise. On the 50th hospital day, blood tests showed a fasting serum triglyceride level within normal limits, but the level began changing rapidly. Eighty days after admission, detailed blood tests revealed decreased plasma LPL (31 ng/mL; reference value, 140–353 ng/mL) and increased serum apo C-II (7.1 mg/dL; reference value, 1.8–4.6 mg/dL), though serum levels of other apoproteins (A-I, A-II, B, and E) were within normal limits. Seven months after admission, plasma LPL level remained as low as 59 ng/mL, though levels of apo C-II (1.9 mg/dL) and triglycerides (139 mg/dL) were within normal limits.

In this case, rapid weight gain and severe hypertriglyceridemia occurred while an attempt was being made to switch from risperidone treatment to olanzapine treatment. Strict diet therapy resolved abnormal laboratory data relatively quickly. Rapidly changed serum triglyceride levels suggested triglyceride metabolism disorder. Detailed blood test revealed decreased plasma LPL levels. However, laboratory data were almost within normal limits for apo C-II and other lipid metabolism parameters. Serum triglyceride levels were within normal limits before the patient received neuroleptics. These findings suggest that decreased LPL did not affect triglyceride metabolism before neuroleptic therapy. They also suggest that the therapy enhanced appetite and that rapidly increased food intake affected triglyceride metabolism, resulting in transient severe hypertriglyceridemia.

Congenital LPL deficiency is inherited in an autosomal recessive manner. Heterozygous disorder of the LPL gene has been reported to reduce LPL and to cause familial combined hyperlipidemia and hypertriglyceridemia.[3] Heterozygous LPL deficiency is unlikely to be affected by daily food intake. The incidence of the deficiency is estimated at 0.2% in the Caucasian population.[3] More than 200 mutations have been identified in the LPL gene.[4] In our case, no genetic analyses were conducted, but decreased plasma LPL suggests heterozygous LPL deficiency.

Many cases of hypertriglyceridemia have been reported as an adverse reaction of atypical neuroleptics.[5,6] Some of these cases may be associated with LPL deficiency. The deficiency seems to be a risk factor for neuroleptic-induced lipid metabolism disorders.

The authors report no financial or other relationship relevant to the subject of this letter.

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A Case Report of Reemergence of Antipsychotic-Induced Dyskinesia With Citalopram

Sir: There is a burgeoning literature associating movement disorders with selective serotonin reuptake inhibitors (SSRIs). However, most of these reports are composed of cases of extrapyramidal symptoms (EPS) such as akathisia, dystonia, and parkinsonism,[1,2] not dyskinesias. Dyskinesias, traditionally associated with antipsychotics, are rare with SSRIs.[1] A case of citalopram-induced reemergence of buccolingual dyskinesia in a patient with a history of antipsychotic-induced dyskinesia is described.

Case report. Mr. A, a 45-year-old man with a history of bipolar disorder (DSM-IV-TR criteria), presented with an exacerbation of depressive symptoms of a month's duration. He had a prior manic episode in September 2002, which was treated with trifluoperazine 15 mg/day and lithium carbonate 900 mg/day for about a year. He developed buccolingual dyskinetic movements with this combination, which resolved completely after trifluoperazine was discontinued. He was maintained on treatment with lithium 900 mg/day for a further 6 months with no recurrence of the dyskinesia. Mr. A's serum lithium level was in the range of 0.6 to 0.8 mEq/L. For the current depressive episode (which occurred about 2 years after the previous manic episode), treatment with lithium carbonate 600 mg/day and citalopram 20 mg/day was started.

On the fifth day of treatment, he again developed buccolingual dyskinesia in the form of repetitive movements of the jaw along with frequent tongue protrusion. He scored 10 on the Abnormal Involuntary Movement Scale.[3] Subsequently, citalopram was discontinued, and Mr. A continued lithium monotherapy with the dose increased to 900 mg/day.

A week after stopping citalopram treatment, Mr. A showed complete remission of the dyskinesia. His depressive symptoms showed some improvement.

Whereas other SSRIs have been implicated in reemergence or induction of dyskinesia, there is no reported association of dyskinesia with citalopram per PubMed (search of English-language publications through March 2007 using the keywords *citalopram* and *dyskinesia*). The temporal relation between the occurrence of buccolingual dyskinesia and treatment with citalopram along with the prompt resolution of the dyskinesia after citalopram discontinuation implicates citalopram in the reemergence of the dyskinesia. Although lithium has also been associated with dyskinesia,[4] it is of interest that it did not cause dyskinesia in our patient when given as monotherapy on 2 occasions. Dyskinesias have been reported with other SSRIs, including fluoxetine, paroxetine, sertraline, and fluvoxamine,[1,2] and in one study comprised 11.3% of the cases of SSRI-induced EPS.[1] While a study showed that citalopram had no effect on preexisting tardive dyskinesia,[5] it has been associated with other movement disorders such as dystonia, tics, and tremors.[6–8] A case report describes withdrawal-emergent dyskinesia with a combination of citalopram and risperidone.[9]

There are no systematic studies of the risk factors for SSRIs either inducing or causing reemergence of dyskinesia. However, individual case reports have mentioned concurrent or prior neuroleptic exposure and preexisting neurologic condition in patients exhibiting this adverse effect.[10–12] Increase in age is also a putative risk factor, while the role of gender is unclear.[1] According to one report, SSRI-associated dyskinesia is subacute in onset and transient in nature,[2] while others cite cases in which it persisted despite discontinuation of the drug.[1] The mechanism of SSRI-associated dyskinesia is unclear but is thought to be serotonin-dopamine imbalance.[1] Other neurotransmitters may also be involved, as suggested by reports of dyskinesias with tricyclic antidepressants that have a predominantly noradrenergic mechanism.[2]

This case raises the possibility of underreporting of the association of SSRIs with dyskinesia and demonstrates a need for more research in this direction.

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A Pilot Observational Crossover Study of QTc Interval Changes Associated With Switching Between Olanzapine and Risperidone

Sir: Antipsychotic drug–related QTc interval prolongations[1–3] have raised concern because of the potential risk of predisposing patients to torsade de pointes and sudden death.[4] Olanzapine and risperidone seem to have similar safety in regard to QTc interval prolongations in clinical trials[5–7] and a head-to-head randomized comparison study.[8] However, risperidone has been reported to be associated with cases of QT prolongation and sudden death.[9–12] Moreover, experimental studies

have found that risperidone prolongs cardiac repolarization by blocking the rapid component of the delayed rectifier potassium current in Chinese hamster ovary cells transfected with the human *ether-a-go-go*-related gene (HERG) potassium channel[13] and is associated with a myocardium-to-plasma concentration ratio that is likely to induce arrhythmia in animals.[14] HERG potassium channel inhibition is commonly used as a screening tool to predict the ability to prolong QT interval.[15]

To date, we have no information on within-subject changes in QTc when the same individuals switch between olanzapine and risperidone. We designed a crossover study to compare the QTc interval changes in patients switching from olanzapine to risperidone or vice versa. This observational crossover study compared the cardiac profiles and metabolic safety associated with olanzapine and risperidone treatment in patients with schizophrenia. The comparison of the lipid and glucose profiles associated with olanzapine and risperidone treatment crossover has previously been published.[16]

Method. Twenty-seven subjects were treated in the routine outpatient setting; all had DSM-IV schizophrenia and had shown poor or partial response to risperidone or olanzapine for at least 3 months, as defined by a Clinical Global Impressions-Severity of Illness scale[17] score of more than 4 (moderately ill). They were willing to change to the other medication (olanzapine or risperidone) and to give full informed consent. Patients with specific medical diseases, such as diabetes mellitus, dyslipidemia, cardiovascular diseases, and hypertension, and patients requiring hospitalization for an acute exacerbation of psychotic illness were not included in this study. The definitions of diabetes mellitus, dyslipidemia, and hypertension were based on those of the International Diabetes Federation.[18] Cardiovascular diseases were assessed by taking a medical history. The institutional ethics review board approved this research, and the study was conducted from January 2004 to December 2005.

For the treatment switch, patients' previous antipsychotic agent was gradually tapered and discontinued over 2 weeks. The clinicians were free to titrate the dose of the second drug according to clinical condition. Concomitant agents, including anticholinergics (biperiden in 2 patients), β-blocker (propranolol in 2 patients), and benzodiazepines (lorazepam in 8 patients, estazolam in 1 patient, and fludiazepam in 1 patient), were kept at the same dose during the study period. No other antipsychotics were coadministered during the preswitch treatment of at least 3 months or for 3 months after the switch.

The standard 12-lead computer-automated electrocardiograph (ECG) series were performed before medication switch and 3 months after crossover. The baseline rhythm, QRS duration, and QT interval were evaluated as the primary step analysis. Repolarization duration variables were corrected for heart rate (with preceding RR interval) using Bazett's formula.[19] All ECG findings were interpreted by an experienced cardiologist (H.-B.H.), who was blind to the treatment group. The paired t test was used to compare ECG profiles for baseline and post-baseline differences using the Statistical Package for the Social Sciences, Version 9.0 (SPSS Inc.; Chicago, Ill.).

Results. Twenty-four patients (10 women and 14 men) with schizophrenia completed this study. The patients' mean age was 36.0 ± 10 years (range, 22–61 years). In the 12 patients taking olanzapine at the time of the study (olanzapine-first group), the QTc interval (393.8 ± 21.0 ms) increased significantly ($p = .019$) after the switch to risperidone (421.6 ± 31.0 ms). In the 12 other patients taking risperidone at the time of inclusion (risperidone-first group), the QTc interval (413.9 ± 15.2 ms) was minimally decreased after the switch to olanzapine (407.7 ± 29.0 ms), and the difference was not statistically significant ($p = .4$). When all patients ($N = 24$) were compared after olanzapine and after risperidone treatment (irrespective of the order), the mean QTc interval was significantly higher ($p = .017$) after receiving risperidone (417.9 ± 24.6 ms) than after receiving olanzapine (400.5 ± 25.6 ms). There were no significant differences in heart rate ($p = .4$), QRS duration ($p = .6$), or QT interval ($p = .055$) when comparing patients after olanzapine treatment and after risperidone treatment (irrespective of the order). No patients had a QTc interval longer than 480 ms during the study period.

There were no significant differences in the mean daily doses of the drugs when they were taken as first or second treatment: the doses of olanzapine were 9.6 ± 4.0 mg for the risperidone-first group versus 10.4 ± 5.4 mg for the olanzapine-first group ($p = .7$), and the doses of risperidone were 3.4 ± 1.7 mg for the risperidone-first group vs. 2.7 ± 1.1 mg for the olanzapine-first group ($p = .2$). The mean ± SD durations of pharmacotherapy prior to switching medications were 16.7 ± 6.3 weeks for the risperidone-first group and 16.3 ± 7.6 weeks for the olanzapine-first group.

To our knowledge, this is the first crossover comparison study of QTc interval changes in the same patients, switching from olanzapine to risperidone or vice versa. The crossover design can minimize the influence of individual variation in cardiac profiles and demographic variables, such as age, sex, concomitant medication use, and personal lifestyles.[16,20] The major finding of this study is that QTc interval increased after patients were switched from olanzapine to risperidone. This is consistent with in vitro studies[9–12] and case reports,[13,14] but not clinical trials.[5–8] The reason for this discrepancy is probably because the crossover study is more sensitive to small differences.[16,20]

This study has some limitations. First, due to the study's observational design, the patients were not free from antipsychotic drugs at enrollment, and the assignment to risperidone or olanzapine as first treatment was not randomized. Second, the dosage of both drugs was not controlled, although there were no significant differences between groups. Third, assessment of QT intervals even by trained cardiologists using state-of-the-art equipment and method is not absolutely reliable,[21] and serum potassium was not measured. Finally, probably due to the small sample size, the decrease of QTc interval in patients switching from risperidone to olanzapine did not reach significance.

Notwithstanding these limitations, our study reveals that in the typical clinical dosages, longer QTc intervals are associated with the use of risperidone compared with olanzapine, especially when switching from olanzapine to risperidone. Unlike other head-to-head comparison studies, our study differentiates the QTc interval change in olanzapine and risperidone. Due to the preliminary nature and the small group of patients in our study, a larger randomized controlled study with a crossover design is warranted.

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Aripiprazole and Worsening of Psychosis: A Case Report

Sir: Crossman and Lindenmayer[1] describe 4 cases of high-dose aripiprazole in treatment-refractory schizophrenia, among which 1 showed improvement and all tolerated the drug satisfactorily. As a counterpoint to that report, we report worsening of psychosis, temporally associated with aripiprazole use, and offer our comments on relapse seen on introducing aripiprazole in the presence of other antipsychotics and thus the need for careful cross-titration at any drug dosage. Aripiprazole is a new atypical antipsychotic with partial D_2- and 5-HT_{1A}–agonist properties and 5-HT_{2A}–antagonist properties. It is a functional D_2-antagonist under hyperdopaminergic conditions, but a functional D_2-agonist under hypodopaminergic conditions. It appears to be generally well tolerated, with a favorable side effect profile.

Case report. Ms. A, a 35-year-old unmarried woman diagnosed with DSM-IV-TR schizoaffective disorder, had been free of psychotic and depressive symptoms for several months while taking amisulpride 400 mg/day. She complained of daytime drowsiness and considerable weight gain over the last 2 years. She requested a change to aripiprazole to reduce sedation and weight gain. Aripiprazole 10 mg/day was commenced alongside amisulpride, with a plan to slowly reduce amisulpride after 2 weeks, increase aripiprazole to 15 mg/day after 4 weeks, and then further reduce amisulpride. Lorazepam 1 mg "as required" was prescribed for agitation.

Nine days after commencing aripiprazole treatment, Ms. A reported some nighttime anxiety, in the absence of sleep disturbance, which was eased by lorazepam. On examination, there were no extrapyramidal side effects, including akathisia. She stopped aripiprazole therapy after a further 3 weeks due to increased anxiety and reemergence of threatening auditory hallucinations. Anxiety lessened 1 week after stopping the drug. However, she appeared distracted and guarded and described increasing persecutory beliefs. Amisulpride was increased to 600 mg/day. Psychotic symptoms continued for 8 to 10 weeks after aripiprazole treatment was stopped, and they then resolved. No significant affective or related psychomotor symptoms were reported or objectively observed throughout any of the aforementioned changes in medication. Although rechallenge with aripiprazole might have clarified the situation, it was felt, in agreement with the patient, to be inappropriate.

Good (i.e., up to 70%) blockade of D_2 receptors achieved by another antipsychotic is likely to create a hypodopaminergic state that allows aripiprazole to act as a dopamine agonist, leading to increased psychotic symptoms.[2–4] DeQuardo[5] felt that enhanced dopamine neurotransmission explained the exacerbation of paranoia and anger observed in his patients, 9 to 28 days after adding aripiprazole 10–15 mg/day to other stable antipsychotic medication.

Up-regulation of dopamine receptors that effectively outstrips receptor blockade by antipsychotics can also result in supersensitivity to dopamine, with emergent psychosis that is resistant to treatment.[6,7] Both tardive dyskinesia and supersensitivity psychosis can arise due to neostriatal and mesolimbic receptor up-regulation, respectively.[8] Supersensitivity psychosis has been reported with D_2-antagonism associated with chronic metoclopramide treatment[9] and withdrawal from chronic antipsychotic use, including atypical antipsychotics.[3,10–12]

A partial agonist may lead to net overstimulation of such a supersensitive system (in contrast to submaximally stimulating

normal systems). Also, when other drugs sufficiently potent to displace a high-affinity partial agonist like aripiprazole are used for breakthrough psychotic symptoms, there is a risk that they may negate the dopamine system stabilization achieved by the partial agonist. Caution is thus a need in both cross-titration and "as required" use of potent D_2-blocking drugs.[7]

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Correction

In the article "Duloxetine Treatment for Role Functioning Improvement in Generalized Anxiety Disorder: Three Independent Studies" by Jean Endicott, Ph.D., et al. (April 2007 issue, pp. 518–524), Table 2 (page 522) incorrectly reported a statistically significant improvement in Q-LES-Q-SF scores for duloxetine compared with placebo in Study 2. Under "Quality of Life and Well-Being" on page 522, the first sentence should read: "Duloxetine-treated patients reported greater improvements in their satisfaction and well-being in multiple life areas as indicated by the Q-LES-Q-SF total score in 2 of the studies (Table 2, $p \leq .001$)." In the Discussion, the second sentence of the second paragraph should read: "In 2 of the 3 studies, duloxetine-treated patients reported greater increases in their total and percent of maximum Q-LES-Q-SF score satisfaction ratings than placebo-treated patients."

The online version of the article has been corrected.