A Crossover Study of Prolactin Changes Associated With Risperidone and Olanzapine

Sir: We read with interest the recent article by Melkersson that described the differential effect on prolactin elevation in schizophrenic patients treated with clozapine (none of the patients had elevated prolactin), olanzapine (24% of the patients had elevated prolactin), and risperidone (89% of the patients had elevated prolactin). Previous head-to-head clinical trials have revealed similar results. However, these comparison studies might be limited by the individual variation in endocrine profiles, demographic variables such as age and gender, and concomitant medication use. We designed a crossover study to compare the prolactin level changes in patients switching from olanzapine to risperidone or vice versa.

Method. This observational crossover study compared the prolactin levels associated with olanzapine and risperidone treatment in patients with DSM-IV schizophrenia. The subjects were treated in the routine outpatient setting and had poor or partial response to risperidone or olanzapine for at least 3 months, defined by a Clinical Global Impressions-Severity of Illness scale score of more than 4 (moderately ill). They were willing to change to the other medication (olanzapine or risperidone) and gave full informed consent. Patients with specific medical diseases, such as diabetes mellitus, dyslipidemia, cardiovascular diseases, and hypertension, and patients who required hospitalization for an acute exacerbation of psychotic illness were not included in this study. The institutional ethics review board approved this research, and the study was conducted from January 2004 to June 2005.

After the new agent was started, the patients’ previous antipsychotic agents were completely discontinued in 2 weeks. The clinicians were free to titrate the dose of the second drug according to the patient’s clinical condition. The 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 fluoxetine in 1 patient), were kept at the same dose in the study period. No other antipsychotics or hormonal treatments were coadministered during the preswitch treatment of at least 3 months or for the 3 months after the switch. Prolactin levels were assessed following overnight (> 12 hours) fasting before medication switch and 3 months after crossover. The paired t test was used to compare prolactin levels for baseline and post-baseline differences with the Statistical Package for the Social Sciences, Version 9.0 (SPSS Inc., Chicago, Ill.). The difference in prolactin level was considered statistically significant if a p value was equal to or less than .05.

Results. Seventeen patients (8 women and 9 men) with schizophrenia completed this study. Their mean ± SD age was 34.9 ± 7.5 (range, 22–46) years. In the 9 patients taking risperidone at the time of inclusion (risperidone-first group), there was a significant (p = .004) decrease in prolactin level after the switch to olanzapine (59.9 ± 38.5 µg/L before switch vs. 13.6 ± 9.7 µg/L after switch). In the other 8 patients (olanzapine-first group), prolactin level was increased after the switch to risperidone (26.1 ± 19.7 µg/L before switch vs. 40.0 ± 16.2 µg/L after switch), but the difference did not reach a significant level (p = .106). When all patients (N = 17) were compared after olanzapine treatment and after risperidone treatment (irrespective of the order), the mean prolactin level was significantly higher (p = .001) in patients receiving risperidone (50.3 ± 31.1 µg/L) than in those receiving olanzapine (19.5 ± 16.1 µg/L). There were no significant differences in the mean doses of olanzapine (10.0 ± 4.3 mg/day for risperidone-first group vs. 8.1 ± 2.6 mg/day for olanzapine-first group) or risperidone (3.7 ± 1.8 mg/day for risperidone-first group vs. 2.6 ± 0.7 mg/day for olanzapine-first group) taken as first or second drugs. The mean ± SD durations of pharmacotherapy prior to the switch of risperidone and olanzapine were 17.3 ± 6.9 weeks and 18.0 ± 9.1 weeks, respectively. However, there was an imbalanced male-to-female distribution between the risperidone-first group (3 to 6) and olanzapine-first group (6 to 2).

To our knowledge, this is the first crossover comparison study of prolactin changes in the same patients, switching from olanzapine to risperidone or vice versa. This study supports an association of elevated levels of serum prolactin with the use of risperidone as compared with olanzapine, which is consistent with the results of most previous head-to-head comparison studies. When patients switched from risperidone to olanzapine, serum prolactin level decreased significantly. This is consistent with the results of Kim and colleagues’ study. However, their study included only female subjects switched from risperidone to olanzapine (not crossover), and the study duration was only 2 weeks.

Our study has some limitations. First, probably due to the small sample size, the increase of prolactin level in patients switching from olanzapine to risperidone did not reach a significant level. Second, due to an observational study design, the patients were not free from antipsychotic drugs at enrollment, the male-to-female distribution between the risperidone-first group (3 to 6) and the olanzapine-first group (6 to 2) was not balanced, the durations of risperidone and olanzapine treatments were not the same, and the assignment to risperidone or olanzapine as first treatment was not randomized. Finally, the dosage of both drugs was not controlled, although there were no significant differences between groups.

Nevertheless, our study clearly showed that in the average clinical dosage, elevated levels of prolactin are associated with the use of risperidone and decrease with olanzapine. On the basis of our findings, we recommend that prolactin should be closely monitored in patients during treatment with antipsychotic drugs, especially with risperidone.

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Recurrent Priapism Associated With Use of Aripiprazole

Sir: Priapism is one of the most serious adverse effects of psychotropic medications. It may be defined simply as abnormally prolonged erection of the penis (or clitoris) that is usually but not invariably painful. Though it is relatively rare as an adverse effect of psychotropic medication, as many as 25% to 40% of priapism cases are attributable to psychotropics.1–2 Treatment of priapism within 4 to 6 hours is important because the condition may cause permanent erectile dysfunction and even penile gangrene. That several of the first-generation antipsychotics may be associated with priapism has been recognized for decades, but a few instances have been reported with all of the second-generation antipsychotics except aripiprazole. In their review, Compton and Miller1 noted priapism to be associated with clozapine, olanzapine, and risperidone. Subsequently, priapism has been attributed to ziprasidone3,4 and quetiapine,5,6 as well. Herein we report what we believe is the first published case of priapism associated with aripiprazole.

Case report. Mr. A, a 47-year-old African American man diagnosed with chronic paranoid schizophrenia 15 years ago, had diabetes mellitus, hypertension, and hyperlipidemia and had been off all psychotropic medication for several years. His outpatient medications were atorvastatin and metformin. He was then prescribed aripiprazole in 2005 by his outpatient psychiatrist, and the first episode of prolonged and painful penile erection started about 6 hours after the first dose of aripiprazole. He was treated at another hospital with intracavernosal phenylephrine, which alleviated the priapism. However, the priapism soon recurred and he presented to our hospital with a painful erection of about 7 hours’ duration. Cavernous irrigation and injection of phenylephrine resulted in prompt detumescence. This treatment was repeated when the priapism recurred 2 days later. The patient refused a shunt procedure for recurrent priapism. He then proceeded to have 3 more episodes over a total of 7 days, even though no additional doses of aripiprazole or another antipsychotic were taken, but responded to cavernal irrigation and phenylephrine each time. In addition, he was put on pseudoephedrine treatment, which has been reported as being helpful for priapism.7

During the hospital stay, the psychosis was quiescent and he was treated with diazepam 15 mg/day only. The patient then remained free of prolonged erections for the next 2 days and was discharged. He was asked to continue pseudoephedrine, apply ice packs to the penis, and abstain from sexual activity. Further monitoring and treatment of his psychiatric condition were deferred to the outpatient psychiatrist. After discharge he was lost to follow-up by us.

No prior incident of priapism had occurred in the patient’s life. He had used cocaine and cannabis in the past, but there was no substance use in the 8 years prior to this admission. The urine drug screen was negative. Diabetes mellitus, hypertension, and hyperlipidemia and the medications atorvastatin and metformin are not known to be associated with priapism. Atorvastatin and metformin have no pharmacodynamic (α-blockade) or pharmacokinetic interaction with aripiprazole. There was no history of sickle-cell disease, perineal trauma, blood-cell dyscrasia, neoplasm, chronic prostatitis, or spider bite, all of which have been associated with priapism.

We used the strategy recommended by Mago7 to be followed prior to publishing case reports. A search of MEDLINE (PubMed) and EMBASE was conducted on January 23, 2006, using the terms aripiprazole and priapism, both as text words and as medical subject heading (MeSH) terms. The only case found in the literature search that was potentially related to the present one was that of priapism developing in a 16-year-old boy upon addition of oxcarbazepine to the patient’s existing regimen of aripiprazole (5 mg/day) and lithium.7 The authors attributed the priapism to oxcarbazepine, and after this was discontinued, the patient continued taking lithium and aripiprazole without further prolonged erections.

The common feature of many medications capable of producing priapism appears to be α-adrenergic blockade, though the fact that medications with no significant α-adrenergic blockade can also be associated with priapism suggests that several different mechanisms may operate. Aripiprazole has significant α1-adrenergic receptor blocking activity.8,9 This consideration and the onset of the condition within a few hours after the first dose of aripiprazole suggest that this drug was indeed the cause of priapism in our patient. The recurrence of priapism several times over a week in this patient can be explained by the long half-life of aripiprazole. The mean elimination half-life for aripiprazole and its active metabolite are about 75 and 94 hours, respectively.10

A variety of psychoactive medications have been associated with priapism. These include antidepressants (selective serotonin reuptake inhibitors, venlafaxine, trazodone, nefazodone, bupropion), anxiolytics (buspirone, hydroxyzine), and antipsychotics (both first-generation and second-generation). Of the second-generation antipsychotics, clozapine, olanzapine, risperidone, ziprasidone, and quetiapine have been reported to be associated with priapism. Our case indicates that aripiprazole should be added to this list. In addition, the case illustrates that when adverse effects due to aripiprazole occur, they may persist for several days due to the long half-life of the drug and its active metabolite, and the patient should be managed and monitored accordingly.

Dr. Mago is a consultant for Bristol-Myers Squibb; has received grant/research support from Bristol-Myers Squibb, AstraZeneca, and...
Intimate Partner Violence Victimization Among Adults With Severe Mental Illness: Results of a Cross-Sectional Study

Sir: There is strong evidence that adults with severe mental illness evidence high rates of both lifetime trauma exposure (particularly physical and sexual abuse) and posttraumatic stress disorder (PTSD) relative to the general population.1 However, little attention has yet been paid in this population to intimate partner violence (IPV), a form of trauma that is often recurrent and linked with long-term mental and physical health consequences.

Method. Data were obtained (but not reported) from a cross-sectional study2 of a random sample of public-sector psychiatric patients recruited from a day-hospital program from 2002 to 2004. A total of 156 randomly identified patients were approached for study participation; 142 provided informed consent, and 141 (79 men, 62 women) completed relevant study measures. We examined rates of adult sexual and physical abuse perpetrated by a romantic partner by using the Trauma Assessment for Adults3 (TAA; for review of psychometrics, see reference 3), as well as characteristics of these assaults (e.g., self-reported fear of being killed or seriously injured at the time of the assault, physical injury, and whether the assault occurred more than once). Due to the nature of the TAA, we did not have the data to assess incidents of IPV perpetration, and thus, we focus exclusively on IPV victimization in our results. We also examined PTSD Checklist4 scores among those with a history of IPV.

Results. Of the final sample, 21 patients (14.9%) reported at least one incident of IPV victimization. Only 1 (1.3%) of 79 men and 20 (32.3%) of 62 women reported a history of IPV victimization. Although not mutually exclusive, 5 (25.0%) of 20 patients (Ns for IPV victimization variables ranged from 19 to 21 due to missing data) also reported physical force or threat of force for unwanted sexual contact, 9 (42.9%) of 21 patients reported a physical assault with a weapon, and 15 (71.4%) of 21 patients reported a physical assault without a weapon by a partner. Seventeen (89.5%) of 19 patients thought they would be killed or seriously injured at the time of the assault, 14 (73.7%) of 19 patients suffered a physical injury, and 14 (73.7%) of 19 patients reported multiple incidents of IPV victimization. The mean (SD) score for those endorsing IPV victimization on the PTSD checklist was 43.57 (19.03), with 8 participants (38.1%) endorsing a score of 50 or above (indicative of PTSD) and 4 (19.0%) endorsing a score between 40 and 49 (clinically meaningful subthreshold symptoms).

A startlingly high number (32.3%) of female public-sector patients with severe mental illness have histories of IPV victimization, and IPV victimization experiences are both recurrent and harmful. These data are notable in that the TAA does not specifically inquire about IPV-related assaults (i.e., the interviewer asks about the perpetrator only after the patient reports a physical or sexual assault), and thus, these rates are likely an underestimate of IPV victimization in this population. Our results are all the more troublesome in light of recent findings by Heru and colleagues5 indicating that over 90% of suicidal inpatients reported a past year history of IPV victimization and perpetration. These findings clearly suggest that the presence of severe and recurrent forms of IPV place individuals with severe mental illness, who already constitute a vulnerable population, at extreme risk. Thus, as public-sector clinicians increase their efforts to screen for trauma and PTSD in this population, particular attention should be paid to assessing for the presence and severity of both IPV victimization and perpetration using more comprehensive IPV measures such as the Revised Conflict Tactics Scales.6

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Dr. Grubauh and Frueh report no additional financial affiliation or other relationship relevant to the subject matter of this letter.

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Internet Assessment of Obsessive-Compulsive Disorder

Sir: The Internet may provide an important and low-cost means to improve communication between patients and clinicians through e-mail and medical information Web sites. In the past year, several reports have also appeared of the successful use of Internet Web sites to help reduce symptoms of anxiety, depression, and phobic avoidance (see, for example, Botella et al.1 and Schneider et al.2).

Here, we report data on Web site usability ratings, as well as age, gender, and OCD severity, from individuals who completed an Internet OCD behavioral assessment.

Method. We developed an Internet Web site for anonymous self-assessment and treatment planning by sufferers of obsessive-compulsive disorder (OCD) that included components from a computerized interactive telephone system called BT-STEPS, which was found in a randomized controlled trial to effectively guide behavioral self-assessment and treatment.1 Print advertisements were placed in a Boston newspaper and the Obsessive-Compulsive Foundation newsletter, and of 111 OCD sufferers who visited the Web site in response to the advertisements, 83 (75%) successfully completed a brief 1-session behavioral assessment (including identification of primary rituals and situations that trigger them, family involvement, and interference with life functioning) and initial behavior therapy treatment plan that they could print out and share with their therapist, if desired.

Results. Although we expected that most visitors to the Web site would be technologically savvy users younger than 30 years, the mean age of completers was 40.4 years (SD = 12.9), and of the 77 users who gave their age, 22 (29%) were aged 40 to 49 years, another 17 (22%) were aged 50 to 64 years, and 3 (4%) were aged 65 years or older. Of 80 subjects answering the gender question, 45 (56%) were female.

All users rated the Web site as either “very easy” or “somewhat easy” to use, and, significantly, ease of use was unrelated to age (r = 0.13, p < .25). Those with more severe OCD (as measured by the Yale-Brown Obsessive Compulsive Scale) were more likely to rate the Web site as “very easy” to use.

Given the shortage of clinicians skilled in effective behavioral treatments for OCD, Internet self-assessment and treatment planning appear to be feasible. Although there remains a substantial “digital divide” in Internet use based on income and education,2 among our assessable respondents, age, gender, and OCD severity were not roadblocks to ease of use of Internet self-assessment. This bodes well for the future acceptance of Web sites containing reliable medical information, since according to a survey, among the next generation of senior citizens—those currently 50 to 64 years old—the Internet has surpassed television, books, magazines, newspapers, and radio as a source of “a lot” of health information.3

Dr. Baer shares intellectual property rights to the BT-STEPS program mentioned in the letter. Dr. Minichiello reports no financial affiliation or other relationship relevant to the subject matter of this letter.

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Hypertriglyceridemia Associated With Direct Effects of Olanzapine Rather Than With Weight Gain: A Case Report

Sir: Hypertriglyceridemia and weight gain are well-documented side effects associated with olanzapine therapy.1 Thus, it has become important to monitor weight and lipid profile including triglycerides in patients taking olanzapine or any other atypical antipsychotic. A total cholesterol level is made up of very-low-density lipoprotein (VLDL), low-density lipoprotein (LDL), and high-density lipoprotein (HDL). Triglycerides are a component of the VLDL portion of the total cholesterol.2 It has been proposed that the lipid changes mentioned above with olanzapine are related to weight gain;3 however, weight gain often does not seem to correlate to the severity of the hypertriglyceridemia observed. The relevance of weight gain to lipid changes remains unclear.4 With both weight gain and hypertriglyceridemia occurring in many cases, it is difficult to delineate the direct effects of olanzapine versus the indirect effects associated with olanzapine-induced obesity. We report a case that demonstrated improvement of hyperlipidemia after olanzapine discontinuation even though the patient continued to be overweight.

Case report. Mr. A was a 22-year-old white man diagnosed with DSM-IV schizophrenia. He had a long history of hospitalizations with a very long index admission, allowing us to view lipid changes over time. Prior to initiation of olanzapine therapy in January 1998, Mr. A had a total cholesterol level within normal range (Table 1), but there were no triglyceride measurements. Olanzapine was initiated, and his total cholesterol level was within normal range (Table 1), but there were no triglyceride measurements.
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Table 1. Medication Doses, Plasma Olanzapine and Lipid Levels, and Weight Changes in Temporal Sequence

<table>
<thead>
<tr>
<th>Olanzapine</th>
<th>Dose Plasma Level</th>
<th>Triglycerides</th>
<th>Cholesterol</th>
<th>Gemfibrozil Dose</th>
<th>Weight</th>
<th>Body Mass Index</th>
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<tr>
<td>Day</td>
<td>(mg/d)</td>
<td>(ng/mL)b</td>
<td>(mg/dL)c</td>
<td>(mg/dL)d</td>
<td>(kg)</td>
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<td>30.5</td>
</tr>
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</table>

*aSome lipid profiles are not described.
*bPlasma olanzapine levels measured within 3 weeks of lipid profile.
*cReference range, 40–160 mg/dL.
*dReference range, 120–200 mg/dL.
*ePatient refused gemfibrozil during some periods.
*fPatient was taking fluphenazine 25 mg/day, which was later decreased and discontinued.
*gPatient was taking benztropine 4 mg/day, which was later decreased and discontinued.
*hDay of first olanzapine dose.
*iDuring short periods of time, the patient agreed to be on a low-calorie diet; most of the time, he refused.
*jThe patient returned to the hospital after 23 days (day 472). During his absence, the patient took no medications.
*kBlood was collected before the patient was given the first 10-mg dose after his return to the hospital.

Abbreviation: AWOL = absent without leave. Symbol: … = not available.

increased. One year after olanzapine initiation, his triglyceride level was 1410 mg/dL, and his cholesterol level was 305 mg/dL (weight = 81.3 kg). Gemfibrozil treatment lowered the patient’s triglyceride level when he was compliant with medication (Table 1).

After 14 months, the patient went away without leave (escaped from the hospital). Upon his return after 23 days with no medication, his olanzapine level was not detectable. His lipids were measured, revealing a triglyceride level of 155 mg/dL and total cholesterol level of 216 mg/dL (weight = 79.5 kg). These lipid levels in the absence of gemfibrozil treatment were some of the lowest lipid levels recorded in the patient since initiation of olanzapine. In the year after Mr. A’s return to the hospital and reinitiation of olanzapine at 35 mg/day, limited changes were seen in his weight (range, 78.5–80.8 kg), but his triglyceride level, in the absence of gemfibrozil, increased to a range of 537 to 729 mg/dL (Table 1).

To our knowledge, this is the first case demonstrating changes in olanzapine’s triglyceridemic effects that were unrelated to weight gain and that were seen following the temporal pattern of presence and absence of olanzapine in the patient’s system. The pattern of olanzapine treatment was on-off-on, while the pattern of the olanzapine-induced weight gain was on-off-on. The patient described in this letter consumed no alcohol during his hospitalization in a closely supervised locked unit, although he reported consuming some beers during his absence from the hospital. He had no signs or symptoms of cirrhosis, nephrotic syndrome, pancreatitis, or other causes of increased triglycerides; thus, in this patient, olanzapine appeared to have a direct effect of increasing triglycerides independent of weight gain.

Hopefully, future research will discern mechanisms of action related to the lipid changes seen with olanzapine and other atypical antipsychotics, allowing for the creation of novel molecules or modifications of current molecules without such deleterious metabolic changes.

This case was published without external support.

In the past 3 years, Dr. de Leon has been on the advisory boards of Bristol-Myers Squibb and Roche Molecular Systems, Inc.; received researcher-initiated grants from Eli Lilly and Roche Molecular Systems, Inc.; and lectured with support from Eli Lilly (once), Roche Molecular Systems, Inc. (5 times), and Bristol-Myers Squibb (once). Dr. Markham Abedi reports no financial or other relationship relevant to the subject of this letter.

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