Aripiprazole Augmentation in Clozapine-Associated Obsessive-Compulsive Symptoms

To the Editors:

Treatment-resistant patients with schizophrenia are frequently prescribed clozapine and a number of authors have reported the possibility that clozapine produces, unmasks, or worsens obsessive-compulsive symptoms (OCS). Results from a recent placebo-controlled trial suggest that the combination of clozapine with aripiprazole in patients with schizophrenia is safe.[1]

We report on 2 patients who developed OCS after starting clozapine and whose OCS cleared after adding aripiprazole.

The first patient is a 32-year-old single unemployed man with disorganized schizophrenia who failed to respond to several antipsychotics including chlorpromazine, clotiapine, haloperidol, quetiapine, and zuclopenthixol at therapeutical doses. The patient showed a very good response to clozapine (200 mg/d), except for the onset of obsessive thinking and control rituals.

This patient did not endorse a history of obsessive thoughts or compulsive behaviors before starting clozapine. His persecutory delusions, bizarre behaviors, and hallucinations cleared approximately 4 weeks after starting clozapine. However, upon beginning clozapine, he started to experience intrusive and unpleasant thoughts that produced uneasiness and apprehension. Specifically, he started to experience thoughts about the possibility that his electric appliances in general, and the espresso machine in particular, would not work appropriately. He clearly understood and recognized that his impression were unreal; however, he felt that he had to act as if his thoughts were correct. He described those thoughts as unwanted, paralyzing, severe, and constantly present. He clearly differentiated such thoughts from the previously experienced delusional thoughts. Although he was able to recognize that the obsessive thoughts were irrational, he was unable to stop thinking about the coffee machine and the only way for him to decrease the anxiety was to call the repair service several times per day.

When a patient presents with both psychotic and obsessive symptoms, it often is difficult to distinguish between schizophrenia, OCD with poor insight, schizophrenia comorbid with obsessive compulsive disorder, or schizophrenia comorbid with medication-induced obsessive symptoms.[2] In our opinion, this patient endorsed the latter diagnosis. Given the concomitant presence of residual negative symptoms, we added aripiprazole 15 mg/d, which was then increased to 30 mg/d. Upon starting aripiprazole, the OCS gradually diminished until complete resolution after approximately 5 weeks.

The second patient is a 39-year-old man with treatment-resistant schizoaffective disorder, who showed a relatively good response to a combination of lithium and clozapine (500 mg/d), except for the onset of obsessive thinking, possibly induced by clozapine. He described the obsessive thinking as involuntary, unpleasant, and seemingly uncontrollable thoughts of racist nature against black people, which caused severe anxiety and fear about possibly being unable to prevent himself from screaming those sentences in front of black persons. Differently from the previously experienced delusional thoughts, the thoughts were perceived and described as unfair, unreal, and unwanted, yet impossible to ignore.

After failing low doses of selective serotonin reuptake inhibitors, which invariably triggered a mixed episode, with dysphoria, increase in substance use, and suicidal tendencies, aripiprazole was introduced (in combination with clozapine) at a dose of 15 mg and then titrated up to 30 mg/d, whereas clozapine was gradually reduced to 200 mg/d. Approximately 1 week after starting aripiprazole, the obsessive thoughts began to be less frequent and intense. The patient perceived and reported a clear improvement and went from spending almost the entire day fighting with those thoughts to spending no more than 1 to 2 hours per day thinking about racist issues and attempting to clear those unwanted thoughts out of his head. For the following months, the intensity and frequency of racist thoughts decreased. However, it took almost 1 year before the thoughts completely cleared, and the possibility that at least a part of the improvement be due to a natural remission of OCS over a prolonged period and/or to a dose reduction of clozapine should be considered.

Our cases confirm other preliminary observations from other authors[3,4] about the possible benefits of adding aripiprazole to clozapine to treat obsessive compulsive symptoms that are caused, triggered, or worsened by clozapine alone. Although a detailed description of the possible hypotheses beyond the exacerbation of OCSs by clozapine and its reversal by aripiprazole augmentation go beyond the scopes of this letter to the Editors, it is likely that serotonergic-dopaminergic interactions play a role and that aripiprazole exerted its beneficial effect via its partial agonism at the D2 and dopamine- and serotonin-stabilizing properties.[5] Large, randomized, placebo-controlled trials to test the risks and benefits of this strategy are warranted.

AUTHOR DISCLOSURE INFORMATION

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Aripiprazole-Associated Leukopenia With Coadministration of Fluoxetine
A Case Report

To the Editors:

Leukopenia and neutropenia may be associated with a range of antipsychotics, mood stabilizers, and selective serotonin reuptake inhibitors, especially clozapine.[1] The same effect has been reported in association with risperidone,[2] olanzapine,[3] quetiapine,[4] and ziprasidone.[5] Aripiprazole is a new second-generation antipsychotic. Its efficacy in schizophrenia seems to be mediated by high receptor affinity of dopamine D_2, serotonin 5-HT_{1A}, and serotonin 5-HT_{2A}.[6] The most common adverse effects of aripiprazole are headache, insomnia, agitation, and anxiety.[7]

Leukopenia has been reported with the use of aripiprazole combined with phenytoin.[8] A decrease in white blood cell (WBC) count induced by the use of aripiprazole alone is much rarer but has been reported for some patients. However, in a case of quetiapine-induced leukopenia, the WBC count returned within the reference range after quetiapine was withdrawn, and substitution of aripiprazole for the quetiapine resulted in maintenance of the WBC count in the reference range with marked reduction in the patient's psychiatric symptoms.[9] Thus, the relationship between the use of aripiprazole and leukopenia requires further elucidation.

Fluoxetine inhibits the liver enzyme CYP2D6, which can increase the plasma levels of drugs metabolized by CYP2D6, such as aripiprazole. The interaction of fluoxetine and other antipsychotics such as clozapine, olanzapine, and risperidone has been described.[10] We report on a patient with no previous history of antipsychotic-associated leukopenia who developed reversible leukopenia with the administration of aripiprazole in conjunction with fluoxetine.

CASE REPORT

A 42-year-old man with a 24-year history of schizophrenia and obsessive-compulsive disorder was admitted to our hospital because of irregular drug adherence and severe psychiatric symptoms. For 1½ years before this admission, he had been treated with several antipsychotics sequentially because of severe psychosis and compulsive behaviors, including quetiapine 600 to 800 mg/d and risperidone 2 to 4 mg/d. Two weeks before this admission, we replaced the risperidone with aripiprazole 10 mg/d. All 3 of the antipsychotics were combined with fluoxetine 60 to 80 mg/d for the compulsive behaviors. The patient had no previous medical history of leukopenia, and his baseline WBC count before initiation of aripiprazole was 5.0×10^9/L. In the beginning of this admission, the WBC count dropped to 4.0×10^9/L. During this hospitalization, the patient was treated with aripiprazole 15 mg/d combined with fluoxetine 80 mg/d for 1 month. Blood testing revealed reduced WBC (3.9×10^9/L) and neutrophil (1.9×10^9/L) counts. Because of worsening auditory hallucination symptoms and compulsive behaviors, the aripiprazole was then increased to 20 mg/d, in combination with fluoxetine 80 mg/d for 28 days. At that point, the WBC count had decreased to 3.0×10^9/L, and the neutrophil count to 1.6×10^9/L. Because of concerns about potential leukopenia, the aripiprazole was tapered from 20 to 10 mg/d over 7 days. Nevertheless, leukopenia and neutropenia developed, with the WBC count decreasing to 2.8×10^9/L and the neutrophil count decreasing to 1.4×10^9/L. Liver function, renal function, C-reactive protein level, erythrocyte sedimentation rate, and results of hematologic morphology examination were normal throughout the course of this hospitalization. The aripiprazole was discontinued, and blood testing 3 days later revealed a return to normal levels for both WBC count (4.6×10^9/L) and neutrophil count (2.5×10^9/L). Because the obsessive behaviors worsened after the discontinuation of aripiprazole, and the relationship between the aripiprazole and leukopenia was still uncertain, aripiprazole 10 mg/d was resumed. Blood testing 1 week later revealed a WBC count of 2.6×10^9/L. Therefore, the aripiprazole was again discontinued. After consultation with the patient's family, we decided to replace the aripiprazole with risperidone 4 mg/d; 2 weeks later, the WBC count had increased to 5.6×10^9/L. However, the patient's obsessive-compulsive symptoms did not improve. Throughout the patient's hospitalization, all blood samples were obtained in the morning to avoid variations related to time of day.

DISCUSSION

In this case, a patient who had previously been treated with risperidone and quetiapine with no related medical problems experienced leukopenia with the administration of aripiprazole in conjunction with fluoxetine. Leukopenia was not present before initiating treatment with aripiprazole, although it has been commonly reported with the use of other antipsychotics, including olanzapine, amisulpride, sulpiride, and ziprasidone. However, aripiprazole is a new antipsychotic agent with differences from other antipsychotics in chemical structure, pharmacodynamics, and pharmacokinetics. This case shows that aripiprazole may be no different from other antipsychotics in the potential to cause leukopenia. One previous report demonstrated an increased risk of leukopenia when beginning aripiprazole in a patient who has previously experienced leukopenia or neutropenia with other antipsychotic treatment, particularly clozapine.[1]

The possibility that fluoxetine is the causative agent in combination treatment with aripiprazole must be considered given a previous report of severe neutropenia caused by fluoxetine.[11] In our case, leukopenia did not occur when fluoxetine was combined with quetiapine or risperidone, occurring only with aripiprazole. Fluoxetine seems unlikely to be the main cause of leukopenia. Fluoxetine and aripiprazole are substrates of cytochrome P450 2A6 (CYP2A6), so the drug-drug interaction may increase the plasma level of fluoxetine to the point of toxicity. A recent study showed that coadministration of aripiprazole did not have a meaningful effect on the pharmacokinetics of fluoxetine and that the enhancement of the antidepressant response is mediated mainly by the adjunctive aripiprazole rather than the increased level of fluoxetine caused by the drug-drug interaction.[12]

Aripiprazole is metabolized mainly by CYP3A4 and the polymorphic enzyme CYP2D6. Some drug-drug interactions have been reported when aripiprazole was coadministered with carbamazepine

(a CYP3A4 inducer) and ketoconazole (a CYP3A4 inhibitor).[13] Fluoxetine, an inhibitor of the liver enzyme CYP2D6, has been associated with increases in the plasma level of aripiprazole, which is metabolized by CYP2D6. The drug interaction of fluoxetine and the other antipsychotics has been described in previous case reports. Coadministration with fluoxetine can increase the plasma levels of 3 antipsychotics: clozapine (metabolized mainly by CYP3D4), olanzapine (metabolized mainly by CYP2D6), and risperidone (metabolized mainly by CYP3D4 and CYP2D6).[10] In previous studies, the use of CYP2D6 inhibitors (fluoxetine or paroxetine) to reduce drug metabolism has been shown to increase serum concentrations of aripiprazole up to 45% compared with controls.[14] Thus, it is possible that in this case aripiprazole levels were unexpectedly higher, but no other adverse effects of aripiprazole were observed. The half-life of aripiprazole is approximately 75 hours, and it needs about 2 weeks to reach a steady-state plasma concentration.[15] This may explain why leukopenia developed even after we reduced the dose of aripiprazole from 20 mg to 10 mg over 7 days. Despite the decrease in the daily dose of aripiprazole, the blood concentration was still greater than the toxic threshold. After discontinuation of aripiprazole, the blood concentration dropped to the safe range, and the WBC count returned to normal within 3 days. The possibility that higher aripiprazole levels may induce leukopenia that was not present at lower levels cannot be excluded. Patients who receive coadministration of aripiprazole and fluoxetine should be closely monitored for effects on WBC and neutrophil counts. However, further studies are needed to elucidate the relationship between leukopenia and drug-drug interactions between aripiprazole and fluoxetine.

CONCLUSIONS

Aripiprazole-associated leukopenia may be caused by combined administration with fluoxetine, a CYP2D6 inhibitor agent. This potential adverse effect may be easily missed, given that WBC count monitoring is not mandatory with use of aripiprazole, unlike with clozapine. Thus, in treating patients with severe obsessive-compulsive disorder as well as schizophrenia, careful monitoring is advisable if a high dosage of aripiprazole is used concomitantly with a CYP2D6 inhibitor agent such as a selective serotonin reuptake inhibitor, especially fluoxetine or paroxetine.

AUTHOR DISCLOSURE INFORMATION

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Perinatal Use of Aripiprazole
A Case Report

To the Editors:

Aripiprazole is a second-generation (atypical) antipsychotic, a class of drugs widely used as first-line therapy for patients with schizophrenia. This drug was licensed in Japan in 2006 and indicated exclusively for treating patients with schizophrenia. Given its favorable efficacy and adverse effect profile, aripiprazole is the first-choice medication for schizophrenia and may be particularly appealing to patients with first-episode psychosis or those who experience adverse effects while taking other antipsychotic medications.[1] To date, only 4 case reports have addressed the safety and efficacy of aripiprazole use during pregnancy.[2–5] These reports provide some clinical reassurance for both mothers and infants.

In this case report, we describe the clinical course of a patient who was given a diagnosis of schizophrenia during pregnancy and was administered aripiprazole. We also report drug levels in the fetus (via cord blood at delivery), mother, and breast milk. Written informed consent for the publication of this report was obtained from the patient.

CASE REPORT

The patient was a 31-year-old Japanese woman in her first pregnancy. Her schizophrenia was diagnosed after the diagnosis of pregnancy. She was referred to our hospital for prenatal care at gestational week 21 when she presented with complications related to untreated schizophrenia. Her symptoms at first visit were

formal thought disorder, persecutory delusions, auditory hallucinations, and a lack of understanding of her disease. It was unclear how long she had been experiencing these symptoms. However, she had been on welfare owing to social and occupational dysfunction for at least several years. Aripiprazole initiated at 22 weeks' gestation at a dosage of 6 mg/d effectively decreased her symptoms of schizophrenia; she gradually gained an understanding of her disease and pregnancy. Her delusions and hallucinations also gradually decreased, allowing us to communicate with her. However, because her delusions and hallucinations still remained, aripiprazole was increased to 12 mg/d at 30 weeks' gestation and to 18 mg/d at 34 weeks' gestation. The dose of 18 mg/d was subsequently maintained.

The patient underwent external cephalic version for breech presentation at 35 weeks' gestation, but this attempt was unsuccessful. She gave birth to a 2866-g boy (median birth weight in Japan, 2863 g; 10th–90th percentile range, 2392–3307 g) by scheduled cesarean delivery at 38 weeks' gestation. No morphological abnormality was observed in the infant. The cesarean delivery was performed under spinal anesthesia without abnormal events. Apgar scores at 1 minute and 5 minutes were 2 and 9, respectively. Blood gas analysis of the umbilical artery revealed a pH of 7.184 and base excess of −5.7. The infant required respiratory support by mask and bag for 1 minute given the lack of spontaneous respiration and poor muscle tone immediately after birth. Spontaneous respiration and muscle tone appeared after 1 minute of respiratory support, and the infant had no subsequent episodes of apnea. Although the patient expressed a desire to breastfeed while continuing aripiprazole at 18 mg/d, she ceased breastfeeding on day 6 after delivery because of significant fatigue from caring for her infant. Her postoperative course was uneventful as was the course of the infant after achieving spontaneous respiration. A follow-up examination at 2 months after delivery showed both mother and baby to be in good health, and patient follow-up has continued at our hospital.

Liquid chromatography revealed aripiprazole concentrations to be 96.4, 181, 7.6, and 38.7 ng/mL in umbilical vein blood at delivery, maternal blood at cesarean delivery, neonatal blood at 6 days of age, and breast milk at day 6 after cesarean delivery, respectively. Coefficients of variation of these measurements were less than 0.05, and the limit of detection was 0.1 ng/mL.

DISCUSSION

Three aspects of the present report are particularly informative. First, this report is unique because it describes the initiation of aripiprazole during pregnancy in a treatment-naive patient with schizophrenia. Second, this is the first report of negative effects in a newborn after birth to a mother receiving aripiprazole, although these negative effects were short-term. Finally, placental transfer and excretion in breast milk were detected based on analysis of drug levels in the fetus (via cord blood at delivery) and breast milk. Furthermore, this is the first report on the placental transfer of aripiprazole.

Drug compliance is very important in the treatment of patients with schizophrenia, especially in the case of a treatment-naive patient. Aripiprazole is reported to be more tolerable than other typical or atypical antipsychotics with regard to adverse effects.[6,7] We chose aripiprazole to treat this patient with the goal of achieving good drug compliance. Major adverse effects associated with aripiprazole are insomnia, tremor, nausea, vomiting, and akathisia.[1] Because our patient did not have these adverse effects, we anticipate she will be able to continue taking aripiprazole uneventfully.

In the present case, the infant did not breathe spontaneously and had poor muscle tone just after birth, although only short-term resuscitation (1 minute) was needed for recovery. It is not clear what caused the infant's initial condition, but we consider 2 possibilities. One is transient placental insufficiency due to spinal anesthesia during cesarean delivery. The other possibility is an adverse effect of maternal drug use because we were able to detect and report for the first time the placental transfer of aripiprazole by measuring its concentration in umbilical cord blood. The concentration (96.4 ng/mL) was almost half that in maternal serum (181 ng/mL). However, because the duration of the infant's poor condition was short, the influence of spinal anesthesia might be the more compatible explanation.

Aripiprazole was present at 38.7 ng/mL in the mother's breast milk; the mother was administered a dose of 18 mg/d. Two of these reports[5,8] presented aripiprazole concentrations in breast milk. In Schlotterbeck's report,[8] aripiprazole concentrations were measured on 2 consecutive days during lactation in a patient administered a dose of 15 mg/d. Aripiprazole concentrations before the intake of medication were 71 ng/mL in plasma and 13 ng/mL in breast milk on day 15 after delivery, and 71 ng/mL in plasma and 14 ng/mL in breast milk on day 16 (ie, milk-plasma ratios of 0.18 and 0.20, respectively). Lutz et al[5] reported that no aripiprazole was detected in breast milk in 3 samples (ie, 24 hours after administration and 30 minutes before the next administration, and 4 and 10 hours after administration) from a patient who received a dosage of 15 mg/d. The result in Schlotterbeck's report is consistent with our value, although we measured the maternal plasma concentration of aripiprazole at cesarean delivery. The concentration of aripiprazole was 7.6 ng/mL in neonatal blood on day 6 after delivery, and the infant showed no adverse symptoms during the neonatal period. However, aripiprazole has a long elimination half-life of 75 hours, even in normal adults.[9] Thus, aripiprazole in the neonate at day 6 might be due to its presence at delivery.

To the best of our knowledge, this is the first published report demonstrating the placental transfer of aripiprazole. However, our findings do not sufficiently address the effects of aripiprazole on mothers and neonates during pregnancy and the lactation period. Further studies will be needed to verify the safety of aripiprazole use in pregnant and lactating women.

AUTHOR DISCLOSURE INFORMATION

The authors declare no conflicts of interest.

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Paliperidone-Related Rabbit Syndrome

To the Editors:

Rabbit syndrome (RS) is an uncommon antipsychotic related movement disorder characterized by stereotyped vertical, rhythmic movements of the perioral muscles at a frequency of approximately 5 Hz, mimicking the chewing actions of a rabbit.[1] RS is believed to be an adverse effect of treatment with first-generation antipsychotics, with reported prevalence ranging from 1.5% to 4.4%.[2,3] However, it also has been reported after treatment with second-generation antipsychotics.[4] Here, we report the first case with paliperidone-related RS.

CASE REPORT

Ms A, a 64-year-old widow, has been diagnosed with schizophrenia for more than 30 years. Since she visited our outpatient department 6 years ago, sulpiride 400 mg per day and clothiapine 40 mg per day were given with stable condition. Approximately 3 years ago, she developed prominent depressive symptoms after the death of her husband; then, the regimen was changed to sulpiride 200 mg per day, clothiapine 40 mg per day, and sertraline 25 mg per day. More than 1 year ago, the regimen of sulpiride was shifted to aripiprazole because of emergence of psychotic symptoms but was rapidly changed to risperidone because of lack of efficacy. In the following months, some extrapyramidal symptoms, such as hands tremor and rigidity occurred, so clothiapine was replaced with zotepine 50 mg per day and risperidone dosage titrated between 1 and 3 mg per day. The regimen was kept for approximately 10 months. However, because she still exhibited overt positive symptoms, such as auditory hallucination, self-talking, and persecutory delusion, paliperidone extended-release (ER) was thereby used to replace risperidone at the dose of 3 mg per day without change of other medications. After 2-month treatment, Ms. A began to experience involuntary rhythmic movements of her mouth, the movements occurred along a vertical axis, being fine and rapid without involvement of the tongue. There were no other significant extrapyramidal symptoms, and neurological examination was unremarkable. The patient was diagnosed with RS, and her score of the subcategory of "lips and perioral area" in the Abnormal Involuntary Movement Scale[5] was 3 points. Paliperidone ER was substituted by olanzapine 5 mg per day with continuous use of zotepine (50 mg/d) and sertraline (50 mg/d). Without the addition of antiparkinsonism agents, RS gradually subsided after 2 weeks of olanzapine treatment. Three months after the regimen, there were no recurrence of psychotic features and RS.

DISCUSSION

Paliperidone was implicated in this adverse effect because of the temporal relation between occurrence of RS and initiation of paliperidone. In this case, zotepine and sertraline were co-administrated during the course; the possibility of RS induced by such polypharmacy could not be ruled out. However, the dosage of zotepine and sertraline remained unchanged for more than 1 year and were continuously prescribed after RS remitted without induction or recurrence of RS; the role of these 2 drugs in RS of this case would be minimal. In addition, we could not rule out the possibility of risperidone withdrawal-emergent RS.[6,7] However, dose reduction of risperidone from 3 to 1 mg per day during treatment course did not induce the emergence of RS; this possibility would be unlikely. To our best knowledge, this is the first case report of RS related to the use of paliperidone. Our case had several risk factors of RS, including being a female patient, older age, and diagnosis of schizophrenia.[6] Rabbit syndrome is similar to the mild oral form of tardive dyskinesia except tongue involvement is spared.[4] To date, there are few case reports of RS induced by second-generation antipsychotics. Most of them were reported to be related to risperidone; the other agents, such as olanzapine, clozapine, quetiapine and aripiprazole, also were mentioned.[6,8]

Paliperidone, an active metabolite of risperidone, is a novel second-generation antipsychotic drug that shares similar but a little different pharmacodynamic profiles from risperidone. For example, paliperidone posits a more potent dopamine D_2 receptor occupancy and weaker serotonin 5-HT_{2A} receptor occupancy than those of risperidone.[9] In our case, RS did not occur under the use of risperidone, but onset after the initiation of paliperidone ER highlights that the incidence of antidopaminergic adverse effects could still differ between risperidone and paliperidone in susceptible patients.

The duration of introduction of second-generation antipsychotics to the onset of RS ranged from 2 weeks to 12 months.[6] Clinicians should watch for the emergence of RS over time after switching to other new antipsychotics.

Although the pathophysiology of RS is not well understood, it may be due to a hypercholinergic state resulting from the blockade of dopaminergic neurons in the extrapyramidal system.[10] Therefore, RS typically responds favorably to anticholinergic agents.[11] However, not all cases responded to anticholinergic drugs. Furthermore, the use of anticholinergics may be followed by the onset of tardive dyskinesia.[6] In our case, RS disappeared while we used olanzapine to replace paliperidone without adding anticholinergics. It is possible that the withdrawal of paliperidone improves the RS; nevertheless, switching to other second-generation antipsychotics seems to be the best strategy for patients with schizophrenia complicated with RS.[12,13]

AUTHOR DISCLOSURE INFORMATION

All authors declare that they have no conflicts of interest.

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Use of Paliperidone in Elderly Patients With Schizophrenia and Schizoaffective Disorder
A Prospective Open-Label Short-Term Pilot Study

To the Editors:

Paliperidone, which is an active metabolite of risperidone, was marketed in the United States in 2006 for the treatment of schizophrenia in adults. Premarketing trials included only patients with schizophrenia and not schizoaffective disorder.[1] Of the 1796 patients included in clinical studies, 125 (7%) were 65 years and older and 22 (1.2%) were 75 years and older. No overall differences in safety or effectiveness were observed between the elderly and the younger subjects (personal communication). Studies of paliperidone use in the elderly, however, are very limited. We have not come across any study of use of paliperidone in elderly patients with schizoaffective disorder. We conducted a prospective open-label short-term naturalistic pilot study to assess the effects of paliperidone in elderly patients with schizophrenia (n = 5) and schizoaffective disorder (n = 6) in inpatients admitted to the geropsychiatry service of St John's Episcopal Hospital in Far Rockaway, NY. Inclusion criteria consisted of patients 60 years and older with a diagnosis of schizophrenia/schizoaffective disorder according to the *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition*, baseline Positive and Negative Symptom Scale (PANSS)[2] score of 70 or higher and baseline Clinical Global Impression (CGI)[3] (Severity) score of 4 or higher. Exclusion criteria consisted of patients with history of allergy to paliperidone/risperidone, patients with current substance abuse as confirmed by toxicology results, patients with preexisting severe gastrointestinal narrowing or severe renal or hepatic impairment, and patients with history of nonresponse to paliperidone or risperidone and current use of risperidone/paliperidone before admission. Efficacy assessments included PANSS, the CGI-S and I scales, and the Montgomery-Asberg Depression Rating Scale[4] (MADRS). The safety measures included the Extrapyramidal Symptom Rating Scale (ESRS),[5] the Drug Attitude Inventory[6] (DAI-10), the QTc interval, pulse, blood pressure and orthostatic blood pressure, and weight assessments. Patients who met the inclusion criteria were enrolled into the study after obtaining informed consent from patient or the responsible next of kin. The study was approved by the institutional review board of St John's Episcopal Hospital. There was a 1- to 3-day washout period. Baseline laboratory tests included complete blood cell count, comprehensive metabolic profile, urinalysis, urine toxicology, electrocardiogram, serum prolactin level, T_3, T_4, and thyroid-stimulating hormone level. Paliperidone was started at 3 mg/d and titrated up to a maximum dose of 12 mg/d at the discretion of the treating psychiatrists. The duration of the trial was based on a naturalistic fashion depending on discharge of the patient or discontinuation from the study for any reasons as determined by the treating psychiatrist. Lorazepam up to a maximum of 8 mg/d was allowed as a rescue medication during the washout period and the duration of the trial.

An intent-to-treat method was used in the analyses of the data, which included all patients who had at least 1 observation during the trial. This analysis in which the last observed score was used as the end point score was considered the primary efficacy analysis. Specifically, to examine medication effects, within-group analyses were also conducted using paired *t* tests to examine changes in paliperidone patients' PANSS, ESRS, CGI, MADRS, and DAI ratings from baseline to end point. Of 15 patients screened, 11 met the inclusion criteria and completed the study. Seven were females. Six patients were diagnosed with schizoaffective disorder and 5 with schizophrenia. Of these 11 patients, 7 were of white and 4 were of African American descent. The mean (SD) age of these patients was 68.27 (5.08) years. The mean dose of paliperidone was 6.9 (1.11) mg/d, and the mean duration of treatment was 17 (5.33) days. All but 1 patient had multiple concurrent medical illnesses and was on concurrent medications for medical problems. The mean number of medical illnesses was 4 per patient. Antipsychotic medications at screening included olanzapine (n = 3), fluphenazine hydrochloride (n = 1), quetiapine (n = 2), ziprasidone (n = 2), and haloperidol (n = 2). One patient was not on any antipsychotic medications at screening. According to the intent-to-treat analyses, 8 (72.7%) of the 11 of paliperidone-treated patients showed a 20% or greater reduction in their total PANSS scores by study end point with the average patient improvement in PANSS total score from baseline to study

end point of 30.09% ± 0.01%. Among the 8 paliperidone patients who met the improvement criterion, reductions in their total PANSS scores ranged from 22% to 44%. The mean and SDs for the PANSS total, positive, and negative symptom subscales at both baseline and end point of medication are presented in Table 1. Paired *t* test comparisons from baseline to treatment end point showed a statistically significant reduction on the PANSS total score ($t_{10} = 8.38$, $P < 0.001$), positive ($t_{10} = 4.88$, $P < 0.001$), negative ($t_{10} = 5.93$, $P < 0.001$), and general ($t_{10} = 10.52$, $P < 0.001$) symptom factors. In addition, CGI scores also significantly improved from baseline to treatment end point ($t_{10} = 5.87$, $P < 0.001$), with a mean (SD) CGI-I of 1.9 (0.53), indicating "very much improved." Paired comparisons for mean MADRAS at baseline assessment (mean [SD], 21.4 [11.06]). to treatment end point (12.3 [9.56]) showed a statistically significant reduction in the MADRS ($t_{10} = 4.49$, $P < 0.001$), with the mean change of 9.03 (6.60) points from baseline to treatment end point. Paired comparisons (baseline vs end point) for paliperidone-treated patients showed a statistically significant reduction in CGI scores from baseline to end point ($t_{10} = 5.87$, $P < 0.001$). The mean (SD) CGI-I was 1.9 (0.53) indicating "very much improved." Paired comparisons of mean ESRS scores from baseline (35.63 [19.94]) to end point (31.63 [17.46]) showed no significant increases on total ESRS score ($t_{10} = 0.45$, $P > 0.05$), with the mean change of 4.00 (29.43). Similarly, no differences were detected in paliperidone treated patients from baseline to end point on any of the ESRS subscales. Results of the ESRS questionnaire indicate $t_{10} = -0.21$, $P > 0.05$: CGI of parkinsonism ($t_{10} = 0.31$, $P > 0.05$), CGI of dystonia ($t_{10} = -0.94$, $P > 0.05$), and CGI of dyskinesia ($t_{10} = 0.01$, $P > 0.05$). Three patients were on antiparkinson medication at screening, and 2 patients were on antiparkinson medication at end point. Mean (SD) DAI scores were 7.4 (2.2) and 8 (1.76) at baseline and at end point, respectively. Baseline and end point data were available only for 10 subjects. There was no discontinuation secondary to safety issues. There was 1 discontinuation secondary to lack of efficacy. This patient received the maximum dose of paliperidone (mean dose, 8.3 mg/d) for the maximum duration (28 days) in this study group. None of the study patients received any rescue medication (lorazepam). The mean prolactin level change from baseline to end point was 68.56 (39.98) ng/mL. However, there were no clinically apparent consequences noted secondary to hyperprolactinemia. The mean QTc change was −13.7 (32.91) milliseconds. The patient with a change of 58 milliseconds had a QTc of 433 milliseconds and heart rate of 105 beats per minute at baseline and a QTc of 491 milliseconds and heart rate of 107 beats per minute at end point. Two patients showed postural systolic blood pressure drop of 29 and 33 mm Hg at baseline and 28 and 23 mm Hg at end point. One patient had a postural systolic blood pressure drop of 72 mm Hg at midpoint. However, none of these patients had any clinical consequences of these changes. Two patients had complained of dizziness without any postural blood pressure changes. The mean change in pulse rate was −3.36 (9.50). The mean weight change was 0.63 (10.54) lbs for the duration of the study. One patient had missing end point weight data. All other laboratory data including complete blood cell count, comprehensive metabolic profile, T_3, T_4, and thyroid-stimulating hormone level did not show any significant changes. There were no deaths in the study group during the hospitalization.

TABLE 1. PANSS Factor Scores at Baseline and at Study End Point

PANSS Factor	Mean	SD	SEM
Positive symptoms—baseline	29.07	5.21	1.44
Positive symptoms—study end point	18.54	3.58	1.08
Negative symptoms—baseline	22.69	6.40	1.77
Negative symptoms—study end point	16.45	4.82	1.08
General symptoms—baseline	51.38	4.92	1.36
General symptoms—study end point	37.09	5.78	1.74
Total symptoms—baseline	103.15	12.11	3.36
Total symptoms—study end point	72.09	11.25	3.39

DISCUSSION

There is paucity of studies examining paliperidone treatment in elderly patients with schizophrenia and none noted with schizoaffective disorder. Tzimos et al[7] conducted a 6-week randomized, double-blind, placebo-controlled study in elderly patients with schizophrenia. Discontinuation rates as well as treatment emergent adverse events were similar between groups. Elevated prolactin levels were noted in approximately half of the patients compared to all patients in our study group, possibly related to the shorter washout period (1–3 vs 5 days) and shorter duration of treatment (17 vs 42 days). The active metabolite of risperidone (9-hydroxyrisperidone) has been found in some studies to be primarily responsible for the hyperprolactinemia secondary to risperidone.[8,9] In the double-blind study, 2 paliperidone patients had serious adverse events (1 with acute coronary syndrome and 1 with mania). Postural hypotension occurred in 4% of paliperidone-treated patients and in 27% in our study group. Of the patients in the study of Tzimos et al, 25% showed a heart rate of more than 100 beats per minute. In our study, the mean change in pulse rate was −3.36. Two patients in the paliperidone group were noted to have a QTc prolongation of more than 500 milliseconds in the double-blind study compared with none in our patients. In our study group, the mean QTc change was −13.7. The use of antiparkinson agents in the double-blind phase end point in the paliperidone group was 17% compared to 18% in our study group. A higher end point score on the DAI Scale correlates with better treatment adherence. The efficacy scales of PANSS and CGI in our study indicate that patients showed a significant improvement after being treated with paliperidone. This is consistent with the results of a previous study that used a geriatric population[7] and that of a recent study on nonelderly adults.[10] Another interesting finding in our study was that the patients showed a significant reduction in depression severity, indicating improvement in patients' mood symptoms during treatment with paliperidone. The previous geriatric study[7] did not use any specific depression scales. However, our results are consistent with the recent study in adult patients[10] with schizophrenia and schizoaffective disorder where the higher-dose group showed significantly greater improvement in symptoms of mania and depression ($P = 0.032$) and the low-dose group showed greater improvement in symptoms of depression. It is possible that the inclusion of patients with schizoaffective disorder in our study group and those in the study of Canuso et al[10] can explain the significant effect on the mood symptoms and indicate paliperidone's utility as a mood stabilizer. Previous studies on risperidone and olanzapine in elderly patients with schizophrenia/

schizoaffective disorder[11–15] have shown that these medications are reasonably effective, but they do have adverse effects like extrapyramidal symptoms, postural hypotension, anticholinergic, metabolic tissues, and cardiovascular problems that need to be closely monitored in the elderly population. The risk factors in the elderly include concurrent medical illnesses and medications and the pharmacokinetic and pharmacodynamic changes. Paliperidone is not approved for the treatment of dementia-related psychosis. The limitations of our study include the small sample size, the open-label design, and the lack of a control group. Paliperidone seemed to be effective in controlling the immediate symptoms of schizophrenia/schizoaffective disorder in the elderly. Patients tolerated the medication without significant adverse events. However, caution should be used in elderly patients with regard to the hypotensive and cardiovascular adverse effects.

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Incidence of Extrapyramidal Syndromes and Tardive Dyskinesia

To the Editors:

In a rare, large, prospective, nonrandomized, open-label study, Novick and colleagues[1] estimated the incidence of extrapyramidal signs (EPS; akathisia, dystonia, parkinsonism) and of tardive dyskinesia (TD) among adults with a diagnosis of schizophrenia and starting or changing antipsychotic treatment. They focused on patients found not to have EPS (n = 4893) or TD (n = 6921) at a baseline assessment; they were then rated for EPS (types or severity unspecified) or TD as present or absent at months 3, 6, 12, 18, 24, 30, and 36. During the 3-year follow-up, the incidence of new cases of EPS ranged from approximately 32.8% with long-acting, injected first-generation neuroleptics, and 26.0% with risperidone, to 8.0% to 14.0% with several modern, second-generation antipsychotics as the nominal treatments. The observed incidence of TD ranged from approximately 9.3% with first-generation neuroleptics, and 6.25% with risperidone, to 3.0% to 11.0% with other modern antipsychotics. This study was a component of a large, international, observational study of psychotic-disorder patients (SOHO) sponsored by Eli Lilly Corporation—manufacturer of olanzapine, the most frequently used antipsychotic in this study.

Although many of the report's findings seem plausible, some potentially important details are not provided, and several questions pertaining to methods and interpretations can be raised. Notably, other psychotropic drugs to which patients had been exposed previously, or may have received during the study, are not reported.[1] The sponsor's product, olanzapine, is suggested to have less risk of EPS and TD than other antipsychotics, including such modern drugs as quetiapine and even clozapine. This conclusion is unexpected and may be misleading. It is not consistent with studies or clinical experience with modern antipsychotics, most of which appear to be similar in risks of adverse neurological effects.[2,3]

TABLE 1. Summary of Findings Reported by Novick et al (2010)[1]

Relative Neurological Risk Levels	Agents	Doses, CPZ-eq mg/d	EPS		TD	
			Patients, n	Incidence, %/3 y	Patients, n	Incidence, %/3 y
High	Neuroleptics	—	536	30.2	732	9.4
Medium	Risperidone	470	994	26.4	1398	6.2
Low	Amisulpride, clozapine, olanzapine, quetiapine	348	3363	8.6	4791	2.9

High-risk agents are first-generation, typical neuroleptics (oral or long-acting and injected); medium-risk is for risperidone (oral); low-risk agents are the other modern antipsychotics listed. Doses are converted to approximate chlorpromazine equivalents (CPZ-eq).[2] Doses and risks of EPSs (akathisia, dystonia, parkinsonism) or TD are based on (subject-number) weighted averages and estimates derived from figures reported.

Potentially important considerations include other psychotropic drugs to which patients had previously been exposed or may have received during the study, information about which is not provided. However, the preintake (baseline) prevalence of EPS was 36.7% (2835/7728), and of TD, 10.4% (807/7728).[1] These rates indicate that patients had been exposed to antipsychotic drugs for some time before the study, but details of previous illness, number of years ill, or of drug exposures and doses are neither provided nor considered in the analyses. As prestudy treatment exposures may contribute to EPS or TD risk, or to decisions about which new treatments to provide, the observed incidences may not generalize, particularly to newly exposed patients, who are not reported separately. Moreover, prior treatments or experiences with adverse effects can bias treatment selections involved, especially in an open-label and uncontrolled study. Moreover, such monotherapy for psychotic-disorder patients would be highly unusual in the current era.[4] As additional treatments and average doses are not specified, it is difficult to ascribe the reported findings simply to effects of sustained monotherapy with the stated, index treatments.

Risk may also be, at least in part, dose dependent. Doses are provided only for second-generation agents at baseline and at 3 years.[1] We estimated 3-year final chlorpromazine-equivalent doses (CPZ-eq mg/d)[5] and corresponding EPS incidence (from the reported Figure 1,[1] because rates and their variances are not provided numerically).[1] These estimated values were for older neuroleptics (no doses provided, 32.8% incidence with depot and 28.0% with oral agents); risperidone (460 mg, 26.4%); and amisulpride (315 mg, 3.7%), clozapine (390 mg, 13.5%), olanzapine (345 mg, 7.7%), and quetiapine (342 mg, 10.9%). The correlation EPS risk and CPZ-eq dose was $r = 0.98$ ($P = 0.004$) and only somewhat less for TD. The possible role of dose was considered, but apparently not included in regression modeling.[1]

In addition, the security of both baseline and semiannually rated, new-onset designations of EPS and TD should be questioned. It appears that EPS and TD were determined to be absent at baseline based on a relatively crude, 1-time assessment.[1] This is an important consideration because manifestations of EPS, and especially of TD, vary considerably over time in individual patients.[6] A history of adverse extrapyramidal effects with other antipsychotics may well have introduced treatment-assignment bias, in which investigators selected drugs of presumably low risk for patients considered to be at higher risk for a recurrence of movement disorders.[7] Without random treatment allocation, it cannot be assumed that the groups were equal at baseline with respect to prior drug-exposures, reactions to these, or for developing EPS or TD. Also, like any open-label trial, there is substantial risk of expectation or detection bias, which often appear to favor a sponsor's product.[8]

For these several reasons, we suggest that the study conclusions might best be limited to categorical estimates of EPS and TD risk for groups of antipsychotic drugs (Table 1). This approach is further supported by our finding that incidence estimates for individual agents between EPS and TD were correlated ($r = 0.84$, $P = 0.02$), so as to support the categorization for both EPS and TD risks. Three EPS and TD risk categories seem to follow from the reported findings: high (long-acting or oral first-generation neuroleptics), medium (risperidone), or low (others). We suggest that more specific quantification, comparisons, and rankings of risk may be unwarranted.

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Reply to Letter on: Incidence of Extrapyramidal Symptoms and Tardive Dyskinesia in Schizophrenia *36-Month Results From the European SOHO Study*

Reply:

Thank you for the opportunity to reply to the letter by Drs Baldessarini and Gardner[1] regarding our paper "Incidence of Extrapyramidal Symptoms and Tardive Dyskinesia in Schizophrenia,"[2] and thanks to Drs Baldessarini and Gardner for their comments. In the paper, we report on the risks of extrapyramidal symptoms (EPS) and tardive dyskinesia (TD) in outpatients with schizophrenia and the factors (including antipsychotic medication) that modify those risks. In their letter, Drs Baldessarini and Gardner note that many of our findings seem plausible, and they refer to our large sample size and 3-year follow-up as study strengths. Drs Baldessarini and Gardner also provide some interesting remarks regarding the analysis of the data.

They mention that some confounding factors (including concomitant medication use, illness severity, years ill, and antipsychotics taken before entering the study) have not been taken into account in the analysis of the dataset. In fact, our analyses did take into account concomitant medication use, illness severity, time ill, and previously untreated status (data on the first 3 variables were provided in Table 2 of our paper), and these were entered in the final statistical model if they were significant predictors. Although we discussed this issue in the manuscript, Drs Baldessarini and Gardner are right to point out that our models did not test the relevance of specific antipsychotics or their doses taken before entering the study. However, this was partly because our analyses only included patients who were not presenting with EPS or TD at study entry, and furthermore, a previous analysis showed no major differences in the medications taken by the patients in the 6 months before entering the study.[3]

Their main criticism is that methodological limitations may limit our estimate of EPS and TD risk for specific drugs. This concern seems to stem partly from an incorrect interpretation of our results. In particular, when summarizing the results of our study, they state that "olanzapine is suggested to have less risk of EPS and TD than other antipsychotics, including such modern drugs as quetiapine and even clozapine." This is not what we concluded in our paper. In the paper, we presented a descriptive analysis and statistical models comparing the risk of EPS and TD between the different antipsychotics. Regression analysis (Table 3 in our paper) showed no significant difference between olanzapine and quetiapine in the risk of EPS ($P = 0.918$) or TD ($P = 0.796$), and we did not conclude at any point that there were significant differences between the 2 treatments. With regard to clozapine, we state that there was a "marginally significant" statistical difference in the risk of EPS ($P = 0.041$) compared with olanzapine but that no difference was found for the risk of TD ($P = 0.367$).

We repeated the analysis of the data including the medication taken during the 6 months before baseline as Drs Baldessarini and Gardner suggested. The results are practically the same as the ones reported in the paper except that the risk of EPS for clozapine becomes marginally nonsignificant: odds ratio (OR), 1.67 ($P = 0.057$) in the new analysis versus 1.73 ($P = 0.041$) in our original analysis. This highlights the dangers of focusing purely on an arbitrary cutoff point for a P value instead of the clinical relevance of the findings.

Drs Baldessarini and Gardner also point out that our analysis did not take into account antipsychotic dose during the 3-year follow-up. As our objective was to report on the risk of TD and EPS in routine clinical practice, we did not focus on dosages because these were decided by the participating psychiatrists. Furthermore, the number of patients taking some medications was low, which impaired the possibility of breaking the medication cohorts into smaller groups based on dose. We have now conducted additional analyses comparing the 2 largest cohorts (olanzapine and risperidone) at different doses. Following the equivalences provided by Gardner et al,[4] we classified the patients into 3 dose groups according to the mean dose during the course of the treatment; low dose (≤10 mg/d olanzapine and ≤3 mg/d risperidone), medium dose (>10 to ≤20 mg/d olanzapine and >3 to ≤6 mg/d risperidone), and high dose (>20 mg/d olanzapine and >6 mg/d risperidone). When comparing patients in each dose group, the differences between olanzapine and risperidone were maintained; the differences between olanzapine and risperidone favored olanzapine in EPS risk: OR, 1.9 ($P < 0.01$) for the low-dose group; OR, 3.8 ($P < 0.0001$) for the medium-dose group; and OR, 3.9 ($P < 0.001$) for the high-dose group. Results were similar for TD: OR, 2.3 ($P < 0.01$) for the low-dose group; OR, 3.0 ($P < 0.001$) for the medium-dose group; and OR, 1.86 (P = NS) for the high-dose group.

Drs Baldessarini and Gardner mention that the use of a single-item measure of each of the adverse events and measurement at 3- or 6-month intervals may reduce the ability to assess these events properly. We acknowledge this limitation in the discussion section of our paper, but its likely effect (together with the prescription of low-risk EPS or TD medications to high-risk patients) is to reduce the magnitude of the differences between medications rather than to create artificial differences.

Finally, Drs Baldessarini and Gardner suggest that "the study conclusions might best be limited to categorical estimates of EPS and TD risk for groups of antipsychotic drugs." We disagree for several reasons. As already discussed, our analysis attempted to control for confounding factors. The paper included a list of limitations to be taken into account when considering the results, and we were cautious when stating the conclusions of the manuscript. The relevance of the manuscript is precisely to highlight that the risks may not be similar for antipsychotics of the same class. Randomized controlled trials remain the gold standard for determining differences between medications, but observational data, such as our paper, can complement clinical trial data and add to the evidence base.

It would be unfortunate if our results on risk of EPS and TD between antipsychotics from an observational study with a lack of randomization to treatment obscured the fact that our paper also explored the nonmedication risk factors. In particular, higher clinical severity at baseline (overall Clinical Global Impression score) predicted a greater risk of developing EPS, whereas the baseline factors of age, EPS, a higher negative Clinical Global Impression score, and gynecomastia were associated with a greater risk of developing TD.

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Amitriptyline and Prochlorperazine Inhibit Proinflammatory Mediator Release From Human Mast Cells
Possible Relevance to Chronic Fatigue Syndrome

To the Editors:

Chronic fatigue syndrome (CFS) is a complex disorder characterized by unexplained severe fatigue for more than 6 months with a broad range of additional symptoms involving the nervous, endocrine, and immune systems and an estimated prevalence of 1%.[1] Tricyclic antidepressants (TCAs) are prescribed off label for a number of painful diseases that often are comorbid, such as CFS, fibromyalgia, interstitial cystitis, and irritable bowel syndrome, the symptoms of which are worsened by stress.[2] However, there is no known mechanism to explain the apparent beneficial action of TCAs.[3]

Mast cells and their mediators have been implicated in inflammatory diseases,[4] including CFS.[5] Mast cells are located perivascularly in proximity to neurons in the thalamus and hypothalamus, especially the median eminence,[6] where they are juxtaposed to corticotropin-releasing hormone-positive nerve processes.[7] Corticotropin-releasing hormone activates mast cells to release vascular endothelial growth factor (VEGF),[8] which could participate in neurogenic inflammation and contribute to the pathogenesis of

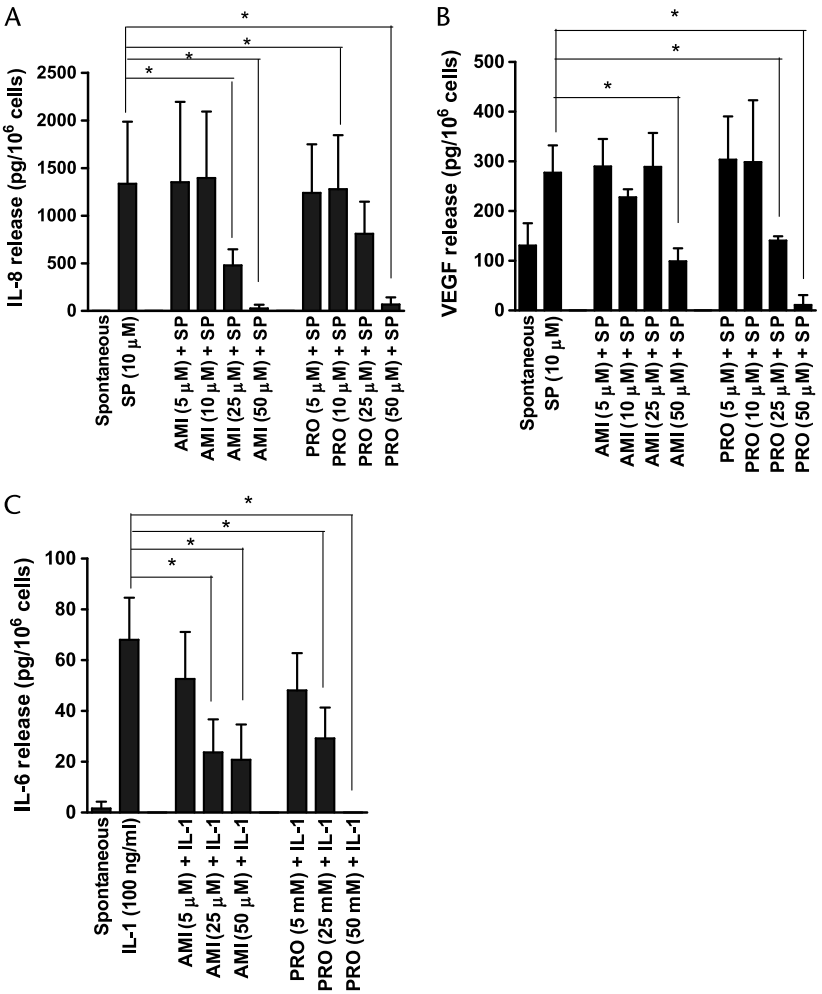

FIGURE 1. Effect of AMI and PRO on SP-induced (A) IL-8 and (B) VEGF release from LAD2 cells, as well as on (C) IL-1–induced IL-6 release from HMC-1 cells. Drugs were added to the cells at the concentrations indicated for 10 minutes before stimulation with SP (10 μM) or before stimulation with IL-1 (100 ng/mL) for 24 hours (n = 3, n = 6). Amitriptyline, bupropion, CIT, tomoxetine, PRO, and SP were dissolved in 0.1% acetic acid and stored at −20°C. All drugs were thawed at room temperature on the day of the experiment. The final concentration of the vehicles did not have an effect (data not shown). The cell viability for all experiments after incubation with the highest concentrations of the drugs tested for 24 hours was greater than 90% by trypan blue exclusion. The LAD2 leukemic mast cells were cultured using StemPro-34 serum-free media (Life Technologies, Grand Island, NY), supplemented with 2 mM L-glutamine, 100 ng/mL recombinant human stem cell factor (rhSCF; Amgen, Thousand Oaks, Calif) and 1% penicillin-streptomycin. The HMC-1 leukemic mast cells were cultured using IMDM (Life Technologies), 5 mL of 1% penicillin/streptomycin, 50 mL fetal calf serum, and 52 μL α-thioglycol). The cultures were used during their logarithmic growth. Interleukins 6 and 8 and VEGF release in cell-free supernatants were measured by enzyme-linked immunosorbent assay (R&D Systems, Minneapolis, Minn). Data presented are mean ± SD (picograms per 10^6 cells) of "net" release (spontaneous release was subtracted before inhibition calculations were performed) from 3 or more experiments (N), each performed in triplicate (n). Results were analyzed with the nonparametric Mann-Whitney *U* test. Statistical significance was set at $P < 0.05$.

CFS. Such mediators may be released locally in the brain or may cross the blood-brain barrier, which can be disrupted by stress, subsequent to mast cell activation.[9] Given the above, we hypothesized that TCAs may be helpful through inhibition of mast cell release of proinflammatory mediators.

The LAD2 human mast cells[10] were cultured mast cells and preincubated for 10 minutes with each one of the following drugs: the tricyclic amitriptyline (AMI), the serotonin-specific reuptake inhibitor citalopram (CIT), the dopamine and norepinephrine reuptake inhibitor bupropion, the specific norepinephrine reuptake inhibitor tomoxetine, and the tricyclic phenothiazine prochlorperazine (PRO), purchased from Sigma-Aldrich (St Louis, Mo), before stimulation for 24 hours with substance P (SP; 10 μM from Sigma-Aldrich).

Amitriptyline (25 and 50 μM) inhibited (Fig. 1A) interleukin (IL) 8 release by 64.2% (from 1334 ± 267 to 478 ± 69 pg/μL) and 98.1% (from 1334 ± 267 to 25 ± 16 pg/μL; n = 3 and n = 6, $P < 0.05$), respectively. Prochlorperazine (50 μM) inhibited SP-induced IL-8 release by 95% (Fig. 1A). Amitriptyline (50 μM) also significantly inhibited SP (10 μM)–induced VEGF release (Fig. 2B) by 64.3% (from 277.4 ± 54.7 to 98.9 ± 26.5 pg/μL; n = 3, n = 6, $P < 0.05$). Prochlorperazine (50 μM) inhibited VEGF release by 96% (Fig. 1B). All other antidepressants had no effect on either IL-8 or VEGF release; cell viability was unaffected (not shown).

In view of the fact that only AMI had any inhibitory effect, we investigated the effect of AMI on mast cell activation by an inflammatory trigger. The LAD2 cells do not synthesize IL-6, whereas HMC-1 cells respond to IL-1 by secreting only IL-6. The HMC-1 cells (1×10^5 cells/200 μL) were preincubated with AMI (5, 25, and 50 μM) for 10 minutes before stimulation with IL-1 (100 ng/mL) for 6 hours (Fig. 1C). Amitriptyline (25 and 50 μM) significantly inhibited IL-6 release by 65.1% (from 68.0 ± 16.6 to 23.7 ± 13.0 pg/μL) and 69.4% (from 68.0 ± 16.6 to 20.8 ± 13.9 pg/μL), respectively (n = 3, n = 6, $P < 0.05$). Prochlorperazine (50 μM) inhibited VEGF release by 100% (Fig. 1C).

In an effort to understand the mechanism of the inhibitory action of AMI and PRO on LAD2 secretion, we investigated their effect on intracellular calcium ions. Substance P rapidly (2 minutes) increased intracellular calcium ion levels that decreased by 20 minutes (Fig. 2). Both AMI and PRO decreased the SP-induced cytosolic calcium increase (Fig. 2).

DISCUSSION

Our findings may be supported by the results of a meta-analysis of fibromyalgia clinical trials that concluded that only TCAs had a large effect on pain reduction, whereas serotonin-specific reuptake inhibitors had a small effect[11]; however, it should be noted that serum antidepressant levels had not been measured to assess patient compliance, and no study controlled for the concurrent consumption of analgesic medications. It is interesting that the tricyclic phenothiazine PRO, commonly used as an antiemetic, also was a potent inhibitor of human mast cell activation. The concentration of AMI and PRO shown here to effectively inhibit mast cell secretion is approximately 10 times higher than what might be expected from the maximal daily dose (eg, assuming 1 compartment model for an 80-kg subject, the AMI maximum dose of 150 mg would yield a serum level of 6 μM). However, brain mast cells may be more susceptible to the action of AMI than the human-cultured LAD2 leukemic mast cells.

The mechanism through which TCAs can inhibit mast cell secretion is still not clear. Here, we show that AMI and PRO can decrease intracellular calcium ion levels. We had previously shown that the inhibitory effect of AMI on rat peritoneal mast cells could be overcome by calcium ions.[12] Other authors had reported that AMI and desipramine (1 μM) partially prevented intracellular calcium increase because of *N*-methyl-D-aspartate in cerebellar granule neurons.[13] The tricyclic phenothiazine chlorpromazine could inhibit the calcium flux because of compound 48/80 in rat peritoneal mast cells,[14] and its inhibitory effect could be overcome by the presence of extracellular calcium.[15]

Mast cells are important for allergic reactions and in immunity[16] and also in inflammatory conditions.[4] In addition to allergic triggers, a number of neuropeptides also can stimulate mast cell secretion including SP.[17] Mast cells secrete numerous vasodilatory and proinflammatory mediators, including IL-6, IL-8, and VEGF. Interleukin 8 was shown to be elevated in the cerebrospinal fluid of patients with CFS.[18] Interleukins 6 and 8 were elevated in the serum of patients with CFS and symptom flare after moderate exercise,[19] whereas another study using multiplex microbead arrays reported high plasma IL-6, low IL-8, and no change in tumor necrosis factor levels in female subjects with CFS at rest as compared with the controls.[20] However, both the source and the methodologies differed between these 2 studies.

The ability of AMI, but not other antidepressants, to inhibit human mast cell release of proinflammatory cytokines may be relevant to their apparent benefit in CFS. Prochlorperazine also may be useful.

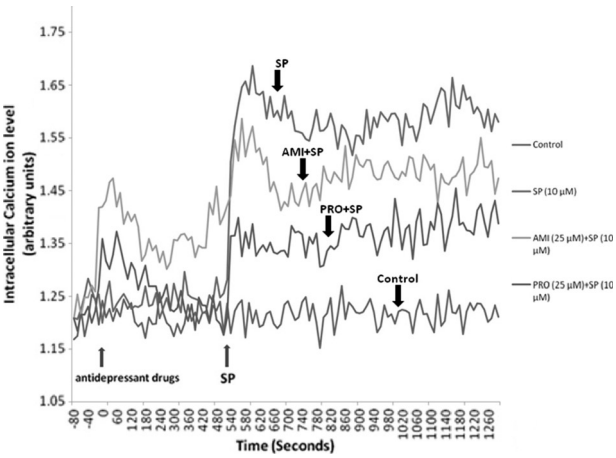

FIGURE 2. Effect of AMI and PRO on LAD2 intracellular calcium ion levels. The LAD2 cells were preincubated with the calcium indicator FURA2 AM (Invitrogen, Carlsbad, Calif) for 20 minutes, washed, and then incubated with either drugs (25 μM) for 10 minutes before addition of SP (10 μM) during which time continuous recordings were obtained at 37°C. Fluorescence was recorded using MDC FlexStation II (Molecular Devices Corporation, Sunnyvale, Calif) at excitation wavelength of 340 nm/380 nm and emission wavelength of 510 nm. The graph is representative of the three similar experiments.

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Baseline Lipid Levels and Acute Treatment Response to Paroxetine and Tianeptine in Depressed Women

To the Editors:

Lipids are essential components of the neuronal cell membrane that regulate electrical properties of the membrane and

expression of proteins (transporters and receptors) embedded in the membrane lipid bilayer.[1] Different psychiatric disorders, including major depression, are associated with altered brain and serum lipid levels.[2–5] Lipids interact with serotonergic system[1] and modulate functional activity of the serotonin transporter,[1] which is a target for numerous antidepressant drugs. The data on the association between the treatment response to antidepressants and basal (pretreatment) lipid levels are scarce.[6] The hypothesis of the present study was that the acute response to paroxetine or tianeptine, 2 effective antidepressants[7,8] with different mechanisms of action,[9,10] would be associated with pretreatment serum lipid levels in patients with depression. Therefore, the aim of the study was to determine pretreatment serum total cholesterol, triglyceride (TG), high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C) levels and clinical outcome, that is, response or nonresponse to 4 weeks of treatment with paroxetine or tianeptine in patients with major depression.

The study included 60 nonsuicidal, nonpsychotic, female inpatients (mean age, 52.6 ± 10.8 years; range, 36–59 years) with major depression diagnosed using a semistructured clinical interview according to *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*, criteria (American Psychiatric Association, 1994). Exclusion criteria were as follows: change (±5%) in body weight in the previous 3 months; use of cholesterol-lowering drugs; hyperlipidemia, pregnancy; lactation; suicidal ideation; alcohol/drug abuse in previous month; other axis I psychiatric disorders; serious medical conditions; additional psychotropic drugs, electroconvulsive therapy, or intensive psychotherapy; and clinical symptoms of hyperthyroidism or hypothyroidism. All patients were medication free for at least 14 days, and 18 patients received no pharmacological treatment for more than 8 weeks. Benzodiazepines were allowed if necessary. The severity of depression was evaluated with 17-item Hamilton Depression Rating Scale (HDRS)[11] before and after 4 weeks of treatment with paroxetine or tianeptine. Responders to treatment had at least a 50% reduction in the initial HDRS scores.

In an open, randomized study, 33 and 27 patients were treated with paroxetine (20 mg/d) and tianeptine (3 × 12.5 mg/d), respectively. Fifteen patients treated with paroxetine and 11 treated with tianeptine were in menopause. All participants signed the written informed consent. The study was approved by the local ethics committee and performed in accordance with the Helsinki Declaration. Before treatment, blood samples were drawn in the morning after an overnight fasting for 12 hours. Serum cholesterol, HDL-C and TG levels were determined by the enzymatic color test for clinical analyzers, with the linearity within concentrations range of 0.64 to 18 mM, 0.05 to 4.65 mM, and 0.11 to 11.40 mM for serum cholesterol, HDL-C, and TG, respectively. Serum LDL-C levels were determined by enzymatic clearance assay, with linearity up to 22.4 mM. The results are expressed as mean ± SD. The statistical evaluation of the data included 1-way analysis of variance (ANOVA), Tukey post hoc test, analysis of covariance with age and menstrual status as covariates, and χ^2 test. The significance was set to $P < 0.05$. The statistical package used was SigmaStat 3.1.

At baseline, patients treated with paroxetine or tianeptine were matched (ANOVAs, $P > 0.05$) on duration of illness (6.2 ± 7.5 or 5.7 ± 6.6 years), number of previous episodes (3.1 ± 3.3 or 3.2 ± 2.2), and duration of the present episode (3.1 ± 1.9 or 2.5 ± 1.1 months). They did not differ ($P > 0.05$) in age (55.6 ± 9.5 or 50.3 ± 12.0 years), body mass index (25.2 ± 3.8 or 25.4 ± 2.7 kg/m^2), and HDRS scores (27.0 ± 2.4 or 26.6 ± 2.0). Baseline serum lipid levels were similar ($P > 0.05$) in patients treated with paroxetine or tianeptine: total cholesterol (5.59 ± 0.84 or 5.80 ± 0.96 mM), HDL-C (1.29 ± 0.37 or 1.27 ± 0.34 mM), LDL-C (3.35 ± 1.17 or 3.86 ± 0.94 mM), and TG (1.64 ± 0.64 or 1.87 ± 0.89 mM). As expected, after 4 weeks of treatment, the total mean HDRS scores differed significantly in responders and nonresponders to paroxetine or tianeptine treatment (Table 1). The frequency of responders and nonresponders was similar ($\chi^2_1 = 2.15$; $P = 0.143$) between both groups. Good therapeutic response was observed in 22 (67%) of 33 paroxetine-treated patients and in 12 (44%) of 27 tianeptine-treated patients. Baseline levels of serum total cholesterol, TG, and LDL-C were significantly higher in nonresponders compared with responders to paroxetine treatment (Table 1), and they were higher than normal values.[3] The significant difference in total cholesterol ($F_{1,31} = 4.98$; $P = 0.033$), TG ($F_{1,31} = 17.32$; $P = 0.003$), and LDL-C ($F_{1,31} = 4.97$; $P = 0.034$) levels persisted when data were adjusted for age and menstrual status as covariates. There were no significant differences in the pretreatment serum HDL-C levels between responders and nonresponders to paroxetine treatment. Baseline lipid levels did not differ significantly ($P > 0.05$) between responders and nonresponders to tianeptine treatment (Table 1).

DISCUSSION

This is the first study that evaluated the association between the entire basal lipid profile and clinical response to paroxetine or tianeptine in nonsuicidal female patients with depression. Our results of the higher baseline cholesterol levels in nonresponders compared with responders to 4 weeks' treatment with paroxetine are in line with the elevated baseline cholesterol levels found in nonresponders to fluoxetine treatment.[6] These data suggest that slightly lower serum lipid profile might indicate a better response to antidepressants, selective serotonin reuptake inhibitors, such as paroxetine or fluoxetine. However, the lipid values detected in our patients, although higher than the recommended lipid levels, were similar to values found in healthy control women of the similar origin.[3]

The possible explanation for the mechanism of the treatment nonresponse in patients with increased cholesterol levels[12] is at present unknown. In our study, responders and nonresponders did not differ in age and were without cardiovascular or cerebrovascular[13] comorbidities that might influence treatment response.[12] We might speculate that the treatment resistance in patients with slightly higher cholesterol values could be due to alterations in serotonergic function because patients with depression and hypercholesterolemia had an attenuated prolactin and cortisol response to DL-fenfluramine,[12] whereas healthy persons with metabolic syndrome had blunted prolactin response to citalopram.[14] Membrane cholesterol could influence synaptic function,[1] including serotonin transporter activity.[1] In turn, some antidepressants have been associated with hypercholesterolemia. In this respect, there is evidence that paroxetine treatment may be associated with increased LDL-C and cholesterol levels.[15]

To the best of our knowledge, there are no data on response to tianeptine and baseline lipid levels. In our study, in contrast to paroxetine treatment, the response to tianeptine was not associated with alterations in baseline lipid levels. Limitations of the study include open design, short follow-up period of 4 weeks and low fixed paroxetine dose of 20 mg daily. In addition, we did not measure paroxetine plasma concentration, and we did not check drug compliance and changes in physical activity. Withstanding these limitations, we did not detect any

TABLE 1. Demographic Data and Pretreatment Serum Lipid Levels in Female Patients With Depression Subdivided Into Responders and Nonresponders to Paroxetine or Tianeptine Treatment

	Paroxetine (n = 33)			Tianeptine (n = 27)		
	Responders (n = 22)	Nonresponders (n = 11)	ANOVA, $F_{1,31}$ *P*	Responders (n = 12)	Nonresponders (n = 15)	ANOVA, $F_{1,25}$ *P*
Age, y	54.7 ± 9.2	54.3 ± 10.6	0.016	51.2 ± 7.5	49.5 ± 15.1	0.120
			0.910			0.732
Body mass index, kg/m^2	24.8 ± 2.7	26.1 ± 3.2	1.437	26.3 ± 2.7	24.7 ± 2.7	2.428
			0.240			0.132
HDRS total scores at baseline	26.1 ± 2.1	27.4 ± 2.9	1.474	26.2 ± 1.9	26.9 ± 2.1	0.897
			0.150			0.378
HDRS total scores after 4 wk	7.1 ± 4.7	22.0 ± 5.0*	9.228	5.5 ± 3.7	25.6 ± 4.8*	11.930
			0.001			0.001
Total cholesterol, mM	5.37 ± 0.78	6.03 ± 0.80*	5.093	5.86 ± 0.55	5.76 ± 1.27	0.066
			0.031			0.800
TG, mM	1.34 ± 0.40	2.12 ± 0.74*	15.504	1.76 ± 0.97	1.96 ± 0.92	0.334
			0.001			0.568
HDL-C, mM	1.35 ± 0.42	1.17 ± 0.22	1.823	1.35 ± 0.43	1.21 ± 0.29	1.059
			0.187			0.313
LDL-C, mM	3.04 ± 1.17	3.97 ± 0.94*	5.258	3.80 ± 0.69	3.90 ± 1.23	0.073
			0.029			0.789

The results are expressed as mean ± SD. The number of subjects is given in parentheses.
*$P < 0.05$ versus matching responders.

significant association between serum lipid levels and response to tianeptine. The preliminary results with paroxetine might indicate that patients with depression and higher than normal baseline cholesterol, TG, and LDL-C levels may be suitable candidates for the initiation or addition of the antidepressant with the mechanism of action different from paroxetine.

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Treatment With Antidepressants Increases Insulin-Like Growth Factor-I in Cerebrospinal Fluid

To the Editors:

The somatotropic axis interacts with the central nervous system on several levels. Growth hormone and insulin-like growth factor I (IGF-I) receptors are expressed in many brain areas including the hippocampus. Insulin-like growth factor I can pass the blood-brain barrier but can also be produced in the brain and thus act via paracrine mechanisms. Insulin-like growth factor I is considered an important factor in the development and differentiation of the central nervous system.[1]

In depressed patients, IGF-I serum and plasma concentrations have been reported to be increased compared to healthy controls.[2–4] Also, the expression of the IGF-binding protein-2 (IGFBP-2), the major brain resident IGFBP, has been found to be decreased in the brain of patients with bipolar disorder compared with controls.[5] Both findings suggest the IGF system to play a role in the pathophysiology of mood disorders.

In rodents, chronic IGF-I treatment leads to antidepressantlike effects in various tests, whereas peripheral anti–IGF-I administration blocks exercise-induced antidepressant effects, which may indicate peripheral IGF-I concentrations to have antidepressant properties.[6] In line with this assumption, increasing unbound IGF-I in the brain is associated with antidepressant and antianxiety effects in rodents.[7] Thus, many beneficial effects of exercise on brain function, including increased hippocampal neurogenesis as well as improved cognition and reduced anxiety, depend on circulating levels of IGF-I.[8] With regard to mechanisms, there is evidence that exercise- and antidepressant-induced enhancement of brain-derived neurotrophic factor (BDNF) depends on IGF-I signaling.[9,10] In addition, intracerebroventricular (ICV) injection of IGF-I in rats produced lasting antidepressantlike effects,[11] which may be mediated by increased levels of serotonin.[12] Therefore, IGF-I being transported from blood to the brain may reinforce the expression of BDNF and thereby contribute to the antidepressant effects of exercise and antidepressant drugs.[13] Although there is some evidence that successful treatment with antidepressants may lower peripheral IGF-I concentrations,[3,4] there is no information on the effect of antidepressant treatment on brain or CSF IGF-I concentrations in humans. Therefore, we analyzed IGF-I concentrations in CSF sampled in unipolar, depressed patients before and during treatment with various antidepressants in the context of 4 different studies.

In this analysis, we included 12 patients with a diagnosis of major depressive episode according to the *Diagnostic and Statistical Manual of Mental Disorders*, scoring 18 points or higher on the Hamilton Depression Rating Scale (HAMD, 21-item version) after a washout period of at least 6 days. Exclusion criteria were lifetime diagnosis of schizophrenia, bipolar or current substance-related disorders, or any other condition known to affect IGF-I levels (pregnancy, anorexia nervosa, chronic kidney/liver disease, or high-dosage estrogen). Only subjects who had given additional written informed consent for the analysis of depression-related peptides in CSF were included. Hamilton Depression Rating Scale ratings were done 1 or 2 days before CSF sampling. Cerebrospinal fluid was sampled at 8.30 under fasting conditions in all subjects. The CSF was sampled on dry ice and immediately stored at −80°C until analysis. None of the subjects received fluoxetine or long-acting injectable antipsychotics before the study. Patients were treated with venlafaxine (150–225 mg) or fixed doses of fluoxetine (20 mg), doxepine (250 mg), or amitriptyline (150 mg). Tricyclics were given at 9:30 PM, whereas fluoxetine and venlafaxine were given at 8:00 AM, except on the day of the second CSF sampling when drugs were given after lumbar puncture. Other psychotropic medication, except lorazepam and zolpidem (during venlafaxine treatment) and chloraldurat (during other treatments), were not allowed.

Insulin-like growth factor I was measured by an IGFBP-blocked RIA as described in detail previously.[14] In brief, CSF was acidified to dissociate IGFs from binding proteins. A highly specific IGF-I polyclonal antiserum (cross-reactivity with IGF-II, <0.05%) was used (sensitivity, 0.03 μg/L; intra-assay variance, <3%).

Pretreatment and posttreatment IGF-I concentrations in CSF were compared

TABLE 1. IGF-I Concentrations and Severity of Depression in CSF Before and After Antidepressant Treatment (HAMD-21 Baseline: After at Least 6 Days of Washout; HAMD-21 Post: After the Indicated Duration of Medication [1/2/4 Weeks]; Final Outcome: After Complete Treatment Period With Given Medication)

No.	Age	Sex	Pretreatment	Medication	Duration (wk)	IGF-I [μg/L] Baseline	IGF-I [μg/L] Post	HAMD-21 Baseline	HAMD-21 Post	Final Outcome With Given Treatment
1	56	F	None	Venlafaxine	4	0.135	0.188	18	4	Remission
2	55	M	None	Venlafaxine	4	0.254	0.306	19	3	Remission
3	47	M	None	Venlafaxine	4	0.228	0.330	21	1	Remission
4	65	M	Not assessed	Fluoxetine	2	0.078	0.368	27	23	Response
5	51	M	Not assessed	Fluoxetine	2	0.219	0.262	24	19	Remission
6	42	M	Not assessed	Fluoxetine	2	0.568	0.387	21	27	Nonremission
7	54	F	Not assessed	Doxepine	4	0.078	0.202	22	25	Remission (add-on sleep deprivation)
8	47	F	Not assessed	Doxepine	4	0.214	0.224	35	26	Remission (add-on haloperidol)
9	48	M	Not assessed	Doxepine	4	0.381	0.503	29	13	Remission
10	50	M	None	Doxepine	4	0.224	0.363	32	21	Nonremission
11	29	F	Not assessed	Amitriptyline	1	0.284	0.334	22	21	Remission
12	67	F	Not assessed	Amitriptyline	1	0.154	0.188	23	22	Nonresponse

using the paired *t* test. Statistical significance was accepted at $P < 0.05$. Results are reported as mean ± SD.

We found a significant increase in IGF-I concentrations in CSF (0.235 ± 0.135 to 0.305 ± 0.096 μg/L) in 11 of 12 patients (Student *t* test: $P < 0.05$; Table 1).

DISCUSSION

To the best of our knowledge, this preliminary analysis is the first to indicate IGF-I concentrations in CSF to increase in depressed patients being treated with various antidepressants.

Preclinical research supports the view that not only systemic treatment with IGF-I[6] but also increased unbound IGF-I concentrations in the brain due to modulation of IGFBP-2 in the brain[7] or ICV injection[11] are associated with antidepressant effects. Moreover, antidepressant effects of tranylcypromine and exercise may depend on IGF-I–mediated activation of the BDNF/tyrosine kinase-B receptor system,[9] although treatment of mice with fluoxetine did not affect hippocampal IGF-I content.[15]

Insulin-like growth factor I serum or plasma concentrations in depressed patients have been found to be increased and to decline in subjects responding to treatment with fluoxetine, amitriptyline, or paroxetine.[3,4] Therefore, it seems surprising that IGF-I in CSF increases during antidepressant treatment. However, it should be considered that IGF-I concentrations in CSF are only approximately 1% of plasma concentrations. Therefore, rather subtle modulation of IGF-I transport in the brain may explain our finding. Moreover, the baseline IGF-I concentrations in CSF were much lower than in adults of similar age, with IGF-I being measured with the same assay (0.51 ± 0.24 μg/L; 14). Therefore, the increased IGF-I concentrations after antidepressant treatment may rather be interpreted as normalized values. Insulin-like growth factor I concentrations in CSF increased in responders as well as nonresponders to treatment. Insulin-like growth factor I concentrations declined in one subject who did not respond to treatment. Of course, the nature of our data does not allow us to conclude whether IGF-I in CSF increases because of transport of IGF-I from blood to brain or because of local synthesis. In most cases, the repeated CSF sampling was done before there was a major change in severity of depression. Thus, changes in CSF IGF-I concentrations during antidepressant treatment may not depend on response to the drugs.

Clearly, our data are very preliminary. First, the sample size is very limited and, thus, it seems important to consider that IGF-I in CSF increased in nearly all patients. Second, patients were recruited during various studies and, therefore, medication and duration of treatments until the second spinal tap were not harmonized. On the other hand, this aspect of our data gives the important impression that the effect of antidepressants on IGF-I in CSF does not depend on the class of medication, long duration of treatment or clinical response. Third, IGF-I concentrations in plasma were only available in a minority of patients (data not reported), which precludes the possibility to study plasma/CSF ratios to get information on blood-brain transport of the protein.

Taken together, although preliminary, our data are the first to support that antidepressants may be involved in the regulation of IGF-I in the brain of depressed patients. Further controlled studies are warranted.

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Efficacy, Safety, and Tolerability of Sertraline on Depressive Symptoms in Women With Comorbid Migraine
An Open-Label Study

To the Editors:

Depression and migraine are each associated with significant disability, and both conditions affect at least twice as many women as men. Large-scale epidemiological studies support a significant association between migraine and depression, with a higher prevalence of migraine diagnosed in depressed patients compared to controls.[1–7] Diagnosis and appropriate treatment of each condition are important for improving outcome, but there are few data on the management of patients with comorbid disease. A 16-week open-label trial of amitriptyline and citalopram, alone or in combination, in patients with comorbid depression, migraine, and tension-type headache prohibited triptans because of concern over risk of serotonin syndrome.[8] After a US Food and Drug Administration warning in July 2006, based on 27 reports of serotonin syndrome in patients prescribed a triptan and an Selective serotonin reuptake inhibitors/Selective serotonin-norepinephrine reuptake inhibitors, US package inserts for triptans and SSRI/SNRIs have included warnings about the potential risk of serotonin syndrome with concomitant use of these drugs.[9] Yet triptans are recommended for the effective treatment of migraine in national headache guidelines.[10] Given that many migraineurs may also require treatment for depression, contraindicating a triptan/SSRI/SNRI combination on the basis of limited evidence may not be in the best interests of the patients.[11] Triptans may also reduce depressive symptoms, independent of antidepressant medication use or psychiatric treatment.[12]

In consideration of these issues, we undertook an open-label concept study to examine the efficacy, safety, and tolerability of sertraline in women with mild/moderate depressive symptoms, treating comorbid migraine with eletriptan. Women attending a specialist headache center aged between 18 and 65 years who were in good general health were invited to participate in a 16-week study. Migraine with or without aura was diagnosed according to the International Headache Society criteria.[13] Eligibility was based on mild to moderately severe depressive symptoms according to the Patient Health Questionnaire (PHQ-9). This self-administered questionnaire consists of 9 items correlating to the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (*DSM-IV*) diagnostic criteria (American Psychiatric Association; 2000). It can be used to detect and quantify the severity of depression: score 0 to 4 signifies minimal depression, 5 to 9 mild depression, 10 to 14 moderate depression, 15 to 19 moderately severe depression, and 20 higher signifies severe depression.[14] Women were not eligible if they had severe depression (PHQ-9 scores $\geq$20) or suicidal tendency, had used antidepressants or migraine prophylaxis for 4 weeks before entry into the study (5 weeks for fluoxetine), had headache on more than 15 days a month, had migraine that was atypical or consistently failed to respond to standard treatments, had contraindications to use of triptans or SSRIs, were pregnant, breastfeeding, or were not using effective contraception. An independent ethics committee approved the protocol. All women gave written informed consent.

Diary data from the month before entry into the study were used to assess baseline number of migraine attacks and migraine days. Women continued daily diary cards to record all headaches/migraine and drugs taken during the study period. Safety and tolerability, number of days of migraine, migraine headache response at 2 hours after the first dose of eletriptan, and use of acute medication throughout the study period were assessed.

At visit 1, women were given a brief physical and neurological assessment and completed the PHQ-9, Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q), and Short Form Health Survey (SF-12). The Q-LES-Q measures levels of satisfaction in key domains of life. Higher scores indicate greater enjoyment or satisfaction in each domain. The SF-12 is a 12-question survey used to monitor quality-of-life outcomes in clinical trials. The 8 domains are combined into 2 main measures: aggregate physical health and aggregate mental health. Treatment was initiated with 50 mg of sertraline daily for depressive symptoms and 40 mg of eletriptan for symptomatic treatment of migraine attacks. A second dose of eletriptan was allowed for recurrence after initial response at 2 hours to a maximum of 80 mg in 24 hours.

Subsequent visits were every 4 weeks. At each visit, adverse events were noted and women repeated the questionnaires. Dose adjustments were discussed, and further eletriptan and sertraline were dispensed. The final protocol visit was 16 weeks after entry. Women who responded to the study medications were able to continue treatment at the end of the study.

Clinical response to sertraline was assessed at each visit based on changes in the PHQ-9 score. If the PHQ-9 score was reduced by 50% or more since the previous visit or was 4 or lower (no depression), no dose adjustments were made. Otherwise, a dose increase of 50 mg was considered, to a maximum daily dose of 200 mg. If unacceptable adverse events occurred, irrespective of response, the dose was reduced by 50 mg to a minimum dose of 25 mg, or the woman was withdrawn from the study. Clinical response to eletriptan was assessed by the response to treatment 2 hours after the first dose. If a woman experienced no unacceptable adverse event but obtained no relief of headache symptoms to mild or absent intensity 2 hours postdose in most of the attacks in the preceding 4 weeks, an increase to a single 80-mg dose per 24 hours was considered. Although the 80-mg dose is off-label in the United States, it is licensed in some countries for patients who have not obtained satisfactory efficacy after an appropriate trial of 40 mg.

The mean scores for each end point (PHQ-9, Q-Les-Q, and SF-12) were obtained at each visit. A paired *t* test was used to examine the difference in scores at the last visit compared to baseline. Changes in scores over time were examined using a repeated-measures analysis with Proc Mixed in Statistical Analysis Software (SAS, Version 8; SAS Institute Inc, Cary, NC). We also examined the change in the proportion of migraine days before and during the trial.

The age range was 24 to 62 years, median was 49 years, and the mean

TABLE 1. Mean Difference in the Percentage of Migraine Days Between the Specified Interval and Baseline

	1–28	29–56	57–84	85–112	Post Study
All Migraine Days					
No. women	51	50	45	43	26
Mean difference (95% CI)	7.4 (3.5–11.4)	8.8 (3.8–13.7)	5.4 (0.7–10.0)	5.8 (1.2–10.4)	1.1 (−5.3 to 7.6)
Moderate or Severe Migraine Days Only					
No. women	51	50	45	43	19
Mean difference (95% CI)	6.4 (2.6–10.3)	6.2 (1.8–10.7)	4.1 (−0.3 to 8.5)	4.8 (0.2–9.4)	−3.1 (−8.3 to 2.1)
Women Who Used Sertraline During the Whole Study					
No. women*	35	35	35	35	21
Mean difference (95% CI)	5.1 (1.0–9.2)	6.3 (2.0–10.6)	6.2 (1.7–10.7)	6.1 (0.8–11.4)	−0.8 (−7.7 to 6.1)

*Analyses exclude 7 women for whom baseline diary data were not available.

baseline frequency of migraine was 3.9 (median, 4.0) attacks per month. Two women withdrew consent before treating. With one exception, all women were using at least one triptan before the study (almotriptan, 3; eletriptan, 6; frovatriptan, 4; sumatriptan, 16; naratriptan, 8; rizatriptan, 2; zolmitriptan, 27). Fifty-eight women started on 50 mg of sertraline and 40 mg of eletriptan. Forty-two women continued sertraline throughout the study. At the final visit, sertraline doses were 25 mg (n = 10), 50 mg (n = 17), 100 mg (n = 12), and 150 mg (n = 3). Nine women withdrew from the study because of adverse events associated with sertraline: 6, because of persistent increased headache (2 at visit 2, 3 at visit 3, and 1 at visit 4); 2, as a result of gastrointestinal disturbance when starting sertraline (visit 2); and one, because of a skin rash when starting sertraline (visit 2). In addition, one woman attended 4 visits and was subsequently lost to follow-up. Twenty-six women continued sertraline after the trial was completed. One woman who stopped sertraline at the end of the study restarted it 7 weeks later and continued for 23 more weeks. The median duration of posttrial follow-up was 35 weeks (range, 17–84 weeks).

Although the study is limited by open-label design, sample size, and short duration, several associations were statistically significant. There was significant improvement in depression and all quality-of-life scores, except physical (mean difference between baseline and final visit: PHQ-9: −4.5 [95% confidence interval [CI], −6.0 to −3.0], $P < 0.0001$; Q-Les-Q: 10.1 [95% CI, 6.3–14.0], $P < 0.0001$; SF12 physical: −3.2 [95% CI, −4.7 to −1.8], $P < 0.0001$; SF mental: 5.8 [95% CI, 3.8–7.8], $P < 0.0001$). From the repeated-measures analysis, there was no evidence of an association between depression or quality-of-life scores and the number of migraine days at baseline (PHQ-9: $P = 0.11$; Q-Les-Q: $P = 0.21$; SF12 physical: $P = 0.10$; SF mental: $P = 0.57$), or with the dose of sertraline (PHQ-9: $P = 0.47$; Q-Les-Q: $P = 0.15$; SF12 physical: $P = 0.76$; SF mental: $P = 0.18$).

There was a significant association between the proportion of days on which a migraine occurred and the duration of treatment with sertraline ($P = 0.005$). The proportion increased during the first 2 months of treatment compared to baseline, followed by a gradual reduction over time (Table 1).

The most common reported adverse events were increased headache, nausea, increased sweating, fatigue, diarrhea, weight loss, and sleep disturbance. These were typically associated with starting sertraline or with an increase in the sertraline dose. Most resolved without intervention. There were no serious or severe adverse events. Increased headache as a subjective assessment (not specified as either migraine or nonmigraine headache) was the most troublesome adverse event, reported by 34 women: 17 when starting sertraline and 21 when the dose of sertraline was increased. In the first 4 weeks after sertraline was started, the mean number of migraine days was increased by 7.4% (95% CI, 3.5–11.4) compared to baseline. Although nonmigraine headache days were not analyzed, the median number of days of increased migraine headache was 21 days (range, 4–88 days) across the study.

We conclude that sertraline was well tolerated, and although there was a potential initial increased risk of migraine headache during the first 3 weeks of treatment, this resolved with continued treatment. These results are in contrast to the Cochrane review in which there were no reports of increased migraine associated with SSRIs and could suggest that migraineurs are more prone to this adverse effect.[15] Because of the nature of the study, we cannot attribute causality. Women who continued in the study experienced a significant improvement in quality of life compared to baseline. When migraine did occur, it was usually successfully treated with eletriptan, as expected from the results of placebo-controlled clinical trials.[16] None of the women reported symptoms that fulfilled the criteria for serotonin toxicity or life-threatening serotonin syndrome based on either the Sternbach or the Hunter criteria.[17,18] Our findings suggest that a blanket contraindication to prescribing the combination of triptans and SSRIs may be excessive, denying effective medication to many women with comorbid migraine and depression.

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AUTHOR DISCLOSURE INFORMATION

E Anne MacGregor has undertaken clinical trials and served on an advisory board for Pfizer Inc (but not within 36 months before submission of this manuscript). The remaining authors reported no relevant disclosures.

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Generalized Action Myoclonus Associated With Escitalopram in a Patient With Mixed Dementia

To the Editors:

Escitalopram is the *S*-stereoisomer of citalopram and a selective serotonin reuptake inhibitor (SSRI). Studies have shown that escitalopram and citalopram produce different effects, possibly because of a lack of contrasting action for *R*-citalopram. However, side effects are quite similar for the 2 drugs and certainly include serotonin toxicity and other effects.[1–3]

We report the case of 78-year-old woman presenting with generalized action myoclonus possibly related to escitalopram intake. Her medical history was significant for coronary disease treated with percutaneous coronary intervention with stenting, previous cholecystectomy, previous isteroannessiectomy for endometrial cancer, insulin-dependent diabetes, hypertension, nonalcoholic hepatic steatosis, and previous left hemispheric transient ischemic attack. During the 3 months preceding her admission, progressive motor and cognitive deterioration had been noted, coupled with wide gradual onset action-related limb jerks. A magnetic resonance brain scan showed both diffuse atrophy and white matter alterations compatible with cerebral chronic ischemic disease. The patient had started escitalopram 10 mg o.d. during this period for treatment of mild anxiety-depression syndrome; she had been on a stable regimen of all of her other medications (aspirin 25 mg, dipiridamol 200 mg b.i.d.; metoprolol 100 mg o.d.; pantoprazole 40 mg o.d.; insulin and nitroglycerine transdermic patch) for at least 1 year. On admission, the patient showed disorientation, hypomimia, limited vertical conjugated gaze, diffuse hyporeflexia, and mild incoordination. Wide base standing and, most importantly, frequent irregular myoclonic jerks at all 4 limbs frankly accentuated by movement were noted. This action myoclonus hindered walking in particular, which was possible only if the patient was supported. The patient underwent a fludeoxyglucose (^{18}F) positron emission tomography brain scan (diffuse hypometabolism), electroencephalogram (not significant), lumbar puncture (normal protein, glucose, and cells; low beta-amyloid 1–42, 399 pg/mL [range, 682–1063]; normal tau, 204 pg/mL [range corrected for age, 66–276]; and low phospho-tau: 18 pg/mL [range, 34.3–53.5]; and absent protein 14.3.3), neuropsychological test battery (frontal and visuospatial deficits compatible with mild dementia), and normal Huntington CAG repeat determination (20/30). Mild diabetic polyneuropathy was confirmed by electroneurography. After removal of escitalopram, the patient showed a slow but progressive improvement of myoclonic jerks. At discharge, 2 weeks later, myoclonic jerks were very mild, and the patient could walk unassisted. Three months later, the patient's myoclonic jerks had disappeared, although mild dementia with mild parkinsonian features was still present.

It is known that some antidepressants may cause a myoclonic phenotype in the absence of other toxicity signs.[4–6] McKeon et al[6] reported 1 patient who experienced resolution of a generalized myoclonus after stopping fluoxetine. In the same case series, circumstantial evidence of long-term use suggested a possible association of myoclonus with SSRI or serotonin-norepinephrine reuptake inhibitors in few additional patients. A link between serotonin overstimulation and myoclonus also is supported by the observation that the latter is present in the serotonin syndrome, a life-threatening condition often related to antidepressant overdose.[3,7] Interestingly, an underlying serotoninergic dysfunction

has already been postulated in neurodegenerative diseases, possibly predisposing to drug-induced movement disorders.[8] Nevertheless, the specific involvement of escitalopram alone in myoclonus has never been described, although its combination with lamotrigine caused this hyperkinesia in 1 previous case report.[9] Few cases implying the association of combined treatment with citalopram and linezolid with myoclonus have been reported as well.[10] In our case, the putative involvement of escitalopram is further supported by the temporal association between resolution of myoclonus and drug withdrawal. Obviously, we consider it highly probable that interacting factors, such as degenerative/vascular serotoninergic dysfunction or the concomitant use of other drugs, might have played an important contributory role. In fact, we might even speculate that this action myoclonus was not simply associated with escitalopram, but resulted either from a subsyndromal condition related to serotonin toxicity that was facilitated by the underlying neurological dysfunction[8] or from an escitalopram-facilitated phenomenon in the setting of a suspected corticobasal degeneration syndrome, whose phenotype encompasses by itself cortical myoclonus. However, both hypotheses lack circumstantial supporting data, and the evidence favors the simple association of myoclonus with escitalopram in the setting of a mild neurodegenerative disorder. We suggest that escitalopram should be probably considered along with other SSRIs as a potential cause of myoclonus, especially in a predisposed neurological setting.

AUTHOR DISCLOSURE INFORMATION

The authors declare no conflicts of interest.

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Psychotropic Medication Use, Hyponatremia, and Falls in an Inpatient Population
A Retrospective Study

To the Editors:

Hyponatremia is a state of excess water relative to sodium in the extracellular fluid compartment.[1,2] This condition is common in inpatient medical populations, ranging between 2.5% and 4.0% (when defined as serum sodium level <130 mEq/L[1]). In a psychiatric population, hyponatremia is found in approximately 4% of patients with chronic schizophrenia and occasionally with other psychiatric disorders.[2] A wide array of psychotropic medications are associated with the risk of hyponatremia through the syndrome of inappropriate secretion of antidiuretic hormone,[1] including selective serotonin reuptake inhibitors (SSRIs),[3,4] to some extent antiepileptic drugs (especially carbamazepine),[4,5] and possibly antipsychotics.[2,5]

It has been suggested that psychiatric disorders are among the clinical conditions associated with increased risk of hyponatremia.[1,2] Other possible risk factors include age[4,6]; concomitant nonpsychiatric medication use, such as diuretics and angiotensin-converting enzyme inhibitors[4,7]; and the presence of medical comorbidities.[4,7] Sex as a risk factor is inconclusive, although female sex was suggested to be a factor in SSRI-associated hyponatremia.[4]

Mild chronic hyponatremia may contribute to an increased rate of falls, likely because of impairment of attention, posture, and gait mechanisms.[8,9] Falls are associated with increased morbidity and mortality rates.[10] To explore the relationship between hyponatremia, falls, and psychotropic medication use, a retrospective chart review was conducted of the patients admitted to the psychiatric inpatient service (94 beds) during the year 2007 at Beth Israel Medical Center, New York. This study was approved by the institutional review board of the facility.

All the cases of hyponatremia in 2007 were identified, and all the admissions with normonatremia in October 2007 were used as controls. Only the first admission was included in the analysis for any patient with multiple admissions. Data on the use of psychotropic medication, age, sex, and falls were collected and included in the analysis. Among the classes of psychotropic drugs analyzed were as follows: SSRIs, antipsychotics, and antiepileptic drugs (AEDs). A particular medication was counted if a patient was consistently taking it until 7 days before the sodium level was obtained or 3 or more doses of medication were given within the past 7 days.

Comparison of each variable between hyponatremic and control subjects was made with the χ^2 test, Fisher 2-tailed exact test, or Student 2-tailed t test. Logistic regression analysis with backward elimination was used to determine the contributing factors to hyponatremia. Covariates

included in the model were age, sex, the use of SSRIs, AEDs, and antipsychotics. A multivariate logistic regression to assess predictors of falls also was conducted. The covariates used in this analysis were existence of hyponatremia, age, sex, the use of SSRIs, AEDs, and antispychotics.

A total of 108 cases (4.84% of admissions) with hyponatremia were identified. Sixteen reports of hyponatremia were excluded because they were later multiple admissions. One case was excluded for unknown medication use, leaving a total of 91 unique cases with hyponatremia (54 male and 37 female patients; mean age, 52.34 ± 17.43 years; mean plasma sodium, 131.82 ± 2.99 mM) to be analyzed.

Of 168 admissions in October 2007, 2 cases were excluded for later multiple admissions, 5 cases for unknown medication use, 2 cases for a serum sodium level not obtained, and 2 cases for hyponatremia, resulting in a total of 157 unique cases for controls (99 male and 58 female patients; mean age, 43.03 ± 15.78) to be included in the analysis.

Mean ages for the hyponatremia and control groups were 52.34 ± 17.43 and 43.03 ± 15.78, respectively ($P = 0.000024$). Interestingly, the use of SSRIs or AEDs were not associated with hyponatremia ($P = 0.21$ and $P = 0.91$, respectively). However, antipsychotic use showed a significant association ($P = 0.011$). Age by each year (odds ratio [OR], 1.03; 95% confidence interval [CI], 1.02–1.05) and antipsychotic use (OR, 1.79; 95% CI, 1.04–3.10) remained as significant predictors of hyponatremia by backward stepwise logistic regression model.

Of the 248 unique cases (91with hyponatremia and 157 with normonatremia), 15 cases fell (8 male and 7 female subjects; mean age, 55.8 ± 13.86), and 233 patients did not fall (145 male and 88 female subjects; mean age, 45.84 ± 17.00). There was a significant difference ($P = 0.027$) in age between the falls (55.8 ± 13.86) and no-falls groups (45.84 ± 17.00). Eleven (12.09%) of 91 hyponatremic cases had falls, whereas only 4 (2.55%) of 157 controls fell ($P = 0.0024$). Here, again, antipsychotic use was associated with falls ($P = 0.0051$). Antiepileptic drug use showed a trend toward association with falls ($P = 0.088$), but SSRI use was not significantly associated ($P = 0.25$). Backward stepwise logistic regression model confirmed that hyponatremia (OR, 4.38; 95% CI, 1.33–14.46) and antipsychotic use (OR, 3.85; 95% CI, 1.17–12.73) were still significantly predictive of falls, whereas the use of AEDs or SSRIs were not. Age was no longer predictive of falls in this model.

Antipsychotic polypharmacy showed a trend toward greater frequency of hyponatremia by t test ($P = 0.058$) and an increase in falls ($P = 0.03$). There was no SSRI polypharmacy, and only 4 patients were on multiple AEDs.

DISCUSSION

This study has confirmed a link between lower sodium levels and falls, but in a group of patients with only minimally reduced sodium levels (131.82 ± 2.99). Other risk factors for falls include age,[11,12] which was confirmed by the results of a t test but was not significantly correlated in a multivariate analysis.

It has long been known that a number of medications can produce syndrome of inappropriate secretion of antidiuretic hormone leading to hyponatremia. SSRIs have been most widely reported as agents that reduce sodium levels.[1,3,4,6,13] AEDs, also extensively used in the treatment of psychiatric disorders, are felt to be another class of medications that have the potential to lower sodium.[1,4,5] Antipsychotics, on the other hand, have been related to hyponatremia mainly in case reports,[6] but there may be a more robust relationship.[2]

In the present study, antipsychotics were found to be a risk factor for falls via hyponatremia, and they also were independently associated with falls. The use of 2 or more antipsychotic medications may result in a greater frequency of both hyponatremia and falls. Surprisingly, SSRIs and AEDs were not related to hyponatremia and falls in this study.

This study has certain limitations. Sample size might be insufficient to detect certain effects. Other possible contributing factors to hyponatremia or falls were not considered, that is, medical comorbidities, substance use, psychiatric diagnosis, and other medications associated with falls such as benzodiazepines, and with hyponatremia such as serotonin norepinephrine reuptake inhibitors and diuretics. Additionally, antipsychotic medications may have produced more cases of orthostatic hypotension than other drug groups, a factor that could have contributed to falls; the rate of hypotension in various groups could not be reliably determined by chart review.

It seems prudent to suggest that inpatients who have mild hyponatremia be placed on fall precautions. This may be particularly true for the elderly. Hyponatremic patients on antipsychotics are especially at risk for falls. Reassessment of the need for antipsychotic medication should be undertaken. The prescription of antipsychotics for sleep, anxiety, and off-label purposes, as well as the use of antipsychotic polypharmacy should be reconsidered in such patients.

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Zuclopenthixol Acetate Treatment in Children With Bipolar Disorder and Severe Aggression

To the Editors:

Pediatric bipolar disorder (BPD) seems to present with atypical features that differ in its presentation from the adult form of the disorder, which complicates its correct diagnosis. The course of the illness in children tends to be chronic and continuous rather than acute and episodic. It is characterized by irritable moods with temper outbursts and often includes threatening or attacking behavior toward family members, teachers, and other children.[1]

In childhood, BPD diagnosis is not as easy as it is in adult form. The major difficulty in diagnosing childhood BPD is its symptomatic overlap and co-occurrence with attention-deficit/hyperactivity disorder (ADHD) and conduct disorder (CD).[2] Normal development and functioning are adversely affected in children with BPD, so early diagnosis and treatment of BPD are critically important.

Practice parameters for childhood BPD suggest mood stabilizers and atypical antipsychotics as first-line treatment. Risperidone,[3] olanzapine,[4] quetiapine,[5] and aripiprazole[6] are the well-studied atypical antipsychotics in childhood BPD, but responses and long-term remission outcomes are not promising. For that reason, in daily practice, combined treatments or some off-label drug regimens are frequent.

Zuclopenthixol is a highly potent thioxanthene neuroleptic agent with combined dopamine-antagonist activity at the D1 and D2 receptors (relatively weaker at D2 receptors). It also has an affinity for alpha-1 adrenergic receptors, a weak affinity for the muscarinic cholinergic receptors, and has no antagonistic activity at serotonin receptor subtypes. Maximum serum concentrations of zuclopenthixol are reached in approximately 4 hours (range, 2–12 hours) after administration.

Zuclopenthixol acetate can be a proper option for reducing severe aggression in children with BPD who are resistant to traditional treatments. Also, it can be used as a drop form that can be mixed into beverages and is edible in case of treatment refusal.

When potential side effects of zuclopenthixol acetate are compared with its beneficial effects, it still remains as a choice that can be applicable for the patients.

In this report, we present 3 children with BPD who have been treated inadequately before and who have shown significant improvement after zuclopenthixol treatment.

CASE 1

Patient A, a 12-year-old boy, had a history of long-standing (nearly 4 years) outpatient treatment with risperidone 2 to 2.5 mg for symptoms of CD. He was first evaluated in September 2004 in response to complaints of relationship problems, fears, behavioral problems, flight of ideas, increased sexual interest, spending too much money, and low school performance. His physical and neurological examinations were normal. He was evaluated with Schedule for Affective Disorders and Schizophrenia for School-Age Children (K-SADS) and diagnosed with BPD according to the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition,* (*DSM-IV*) criteria. At the beginning of the treatment, Young Mania scores were found to be 39.

There had been a partial improvement with his previous risperidone therapy, up to 3 mg. He had weight gain after the risperidone treatment; therefore, we switched to quetiapine monotherapy with 25 mg/d and increased to 50 mg/d. During this period, his BPD symptoms aggravated, and he refused the treatment. So, zuclopenthixol treatment was given with 1 drop twice a day (2 mg). After 3 weeks, he was more willing to attend his school and showed a better performance, but his talkativeness, sexual interest, lying, and spending too much money continued. His zuclopenthixol dosage was increased to 4 drops twice a day (8 mg) gradually, and there was a significant improvement in his clinical situation after that. During the observation, we decreased the zuclopenthixol dose to 1 drop twice a day (2 mg). Consequently, patient A's mood has been stable for 6 months. His Young Mania scores decreased to 15 after treatment.

CASE 2

Patient B, an 8-year-old boy living with his stepparents, was referred to our clinic with severe aggression toward his teachers and friends in kindergarten. The boy's behavior expressed with irritability, school problems, fears, telling lies, mood liability, outbursts, hyperactivity, oppositionality, vindictiveness, and negativistic and hostile behaviors. He was evaluated with K-SADS and diagnosed with CD + BPD + ADHD according to the *DSM-IV* criteria. With risperidone (1 mg/d) and osmotic-release oral system long-acting methylphenidate (OROS, MPH) (36 mg/d) treatment, there was no significant improvement, so valproic acid (500 mg twice a day) was added. His clinic symptoms got better, but his temper tantrums still continued. Risperidone treatment was stopped and switched to olanzapine (20 mg/d); however, there was still no response, and complaints persisted after 2 atypical antipsychotics and stimulant treatment. At last, olanzapine was stopped, and zuclopenthixol 2 drops twice a day (4 mg) were added; however, his behavioral problems were uncontrolled, so we increased the dosage to 4 drops twice a day (8 mg). Currently, patient B is attending his first class and is staying on 6 mg/d of zuclopenthixol, MPH (OROS) (36 mg/d), and valproic acid (500 mg twice a day). His mood remains euthymic and has been stable for 3 months. At the beginning of the treatment, his Young Mania scores were found to be 30 and decreased to 13 after treatment. Also, Turgay *DSM-IV* Based Disruptive Behavior Disorders Scale scores were revealed to be 14 for hyperactivity and 12 for oppositional disorders. After treatment, the scores decreased to 6 and 4, respectively.

CASE 3

Patient C, a 12-year-old boy living with his parents, was first evaluated in

March 2007. When he came to us, he was still under treatment with clomipramine (75 mg/d), risperidone (1 mg/d), and MPH (OROS) (18 mg) with a diagnosis of obsessive compulsive disorder + ADHD + CD. Although his obsessions were reduced with clomipramine, his behavioral problems continued. He showed severe aggression, although his dosage of risperidone was increased. During the observation, his violence toward his mother and friends, spending too much money, and sleep disturbances were aroused. He was evaluated with K-SADS. A presumptive diagnosis of BPD was made according to *DSM-IV.* After risperidone treatment was stopped, zuclopenthixol was added (1 drop twice a day, 2 mg) to his existing therapy. Currently, patient C's mood is stable, and his aggressive behaviors have been abated for approximately 8 months. At the beginning of the treatment, his Young Mania scores were found to be 30 and decreased to 10 after treatment.

DISCUSSION

In this report, we described 3 pediatric patients with BPD who showed significant improvement after switching to zuclopenthixol treatment. There were partial improvements and experience of adverse effects with their previous atypical antipsychotics and mood-stabilizing agents. Zuclopenthixol can be used in children with BPD and severe aggression and also when oral medication is refused, as seen in one of our cases that we present here. It can be an alternative treatment with its drop form which can be mixed with food.

Although the prevalence of BPD in childhood is undefined, retrospective studies with adult BPD has shown the onset of this complex disorder to be frequent in childhood. Symptom presentations and patterns of illness vary from the classic descriptions of BPD in adults. Childhood BPD is characterized with nonepisodic, rapid cycling, increased irritability, less euphoria, grandiosity, and mixed episodes, and patients are more likely to have comorbid ADHD and CD. The cases we present here also had comorbid situations that were diagnosed in their early clinical applications, and then, they were admitted as having BPD symptoms during the observation. Traditional mood-stabilizing agents or atypical antipsychotics are the first-line treatment in this population, but poor efficacy, intolerable side effects, or treatment refusal causes difficulties for clinicians, so combination therapies or off-label drugs may be used.

There is a lack of literature about using zuclopenthixol acetate on the pediatric population. Spivak et al[7] reported an open-label study about the efficacy and safety of zuclopenthixol in the treatment of behavioral disturbances in mentally retarded children and adolescents. In their study, a sample of 15 children and adolescents with mental retardation (11 male and 4 female subjects) aged 5 to 18 years, all exhibiting severe behavioral disturbances, were evaluated. After a washout period from previous antipsychotic agents (haloperidol, perphenazine, and clotiapine), they started zuclopenthixol monotherapy treatment. The initial dose was 2 mg/d and was increased every 2 days according to the clinical response, up to the maximum dose of 26 mg/d. There had been a significant improvement in aggressive behavior, hyperactivity, and temper tantrums after 12 weeks of zuclopenthixol treatment.

In our cases, partial improvements with generally accepted treatment choices and impairment in their clinical situations as a result of disruption and refusal of the previous antipsychotic treatment encouraged us to administer an "off-label drug" zuclopenthixol, which has not been commonly used in the pediatric population. Most studies with adult patients have demonstrated that zuclopenthixol is an effective treatment for acute psychotic illness. Decreased aggressive behavior and agitation are signs of the effectiveness of zuclopenthixol.[8,9] In line with these findings derived from adult studies, the cases we present here also showed decreased agitation and sedation after a very short period of zuclopenthixol administration. The sedative property of zuclopenthixol made it useful for these patients in an acute period occurring with agitation, irritability, and aggression. After stabilizing the moods of these children, we continued zuclopenthixol treatment to maintain their improvement.

These cases are composed of preliminary information about the efficacy of short-term zuclopenthixol treatment in pediatric BPD. Further studies, particularly placebo controlled and double blind, are indicated to better define the clinical use of zuclopenthixol in the treatment of children with pediatric BPD.

AUTHOR DISCLOSURE INFORMATION

Dr Eyup Sabri Ercan stated that he is in the advisory boards of Lilly and Janssen-Cilag. Drs Akyol Ardic, Kandulu, and Yektas have no conflict of interest.

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An Importance of Dose in Antipsychotic Combination Therapy for Schizophrenia

To the Editors:

I read with great interest an important contribution by Lin et al[1] in which they compared risperidone 4 mg (monotherapy) versus risperidone 2 mg plus haloperidol 2 mg (polypharmacy) in a randomized double-blind fashion among patients with short-term exacerbation of schizophrenia for 6 weeks. They found similar efficacy for both groups, although monotherapy was associated with a higher score in the Simpson-Angus scale, higher prolactin levels, and greater use of anticholinergic biperiden. Several issues, however, need to be pointed out in interpreting their precious findings.

First, the authors noted that risperidone 1 mg is arguably equivalent to haloperidol 1 to 2 mg; dose adopted is a highly pertinent factor. While noting a potential problem in dose equivalence (across typical and atypical antipsychotics in particular), the authors assumed an equal equivalency of risperidone and haloperidol in this study. However, it is indicated that experts assume that risperidone 2 mg is equivalent tohaloperidol 3.5 mg.[2] A more recent expert survey revealed with high confidence a similar equivalency ratio between risperidone 1 mg and haloperidol 1.67 mg.[3] As such, it may have been more reasonable to compare risperidone 3 mg versus risperidone 2 mg plus haloperidol 2 mg (or risperidone 4 mg vs risperidone 2 mg plus haloperidol 3.5 mg). This subtle but critical issue may be the reason of their observation of higher parkinsonism scores and resulting greater use of biperiden as well as higher prolactin with monotherapy.

Second, the authors exclusively recruited newly admitted patients with short-term exacerbation and they seem to conduct the entire study on an inpatient basis. Although it is plausible that monotherapy was greater in drug cost (as newer antipsychotics are usually more expensive), much more of the cost would be reasonably attributable to hospitalization. Even a few days' difference in admission would offset a relatively minor cost of medications or may even be cost saving. In light of this perspective, because many patients would have reasonably improved and would have been ready for discharge before the end of the study (as is inferred from the original Figure 1[1] that depicts a typical curve of improvement), their comment on cost should be appreciated with caution. Finally, it seems useful to present actual scores on the Positive and Negative Syndrome Scale, the Clinical Global Impression—Severity Subscale, and the Global Assessment of Functioning at the baseline so that readers can have a better interpretation and sense on generalizability of their crucial observation.

Clinically, if adverse events such as extrapyramidal symptoms become a problem, the dose of antipsychotics would be reduced in response (although another possibility is to use antidotes such as anticholinergics against parkinsonism). If doses were adequately counterbalanced (eg, risperidone monotherapy was used at 3 mg and not 4 mg), their negative findings with monotherapy on the aforementioned aspects that may be dose dependent[4] might have disappeared. Taken together, contrary to their conclusion that more studies are necessary to evaluate the effectiveness of risperidone and haloperidol combination in schizophrenia, their results seem to argue against combination therapy—also important to note is that there are practically too many possible antipsychotic combinations with dose in mind that remain unexplored. Rather, more efforts would be indicated to evaluate the relative effectiveness of antipsychotics in schizophrenia in general[5] or to target specific treatments in a subgroup of patients (eg, very challenging population).[6,7]

AUTHOR DISCLOSURE INFORMATION

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Reply to Comments by Dr Suzuki on "A Randomized, Double-Blind Comparison of Risperidone Versus Low-Dose Risperidone Plus Low-Dose Haloperidol in Treating Schizophrenia"

Reply:

We are replying to a letter to the editors that commented on our article.[1] The antipsychotic-equivalent dosages should be considered approximate. For example, the dose equivalent of haloperidol to chlorpromazine ranges from 50 mg[2] to 60 mg.[3] Our hypothesis is that an antipsychotic drug combination of low-dose risperidone plus low-dose haloperidol is similar to regular-dose risperidone monotherapy in efficacy and safety for treatment of schizophrenia. Regardless of risperidone 1 mg equivalent to haloperidol 1, 1.67, or 2 mg, low dose of haloperidol is supposed to replace the comparable dose of risperidone and achieve a favorable clinical response and adverse-effect profiles.

TABLE 1. Comparison of Groups in Baseline Measures

	Risperidone (2 mg/d) + Haloperidol (2 mg/d)			Risperidone (4 mg/d)			
Variable	**n**	**Mean**	**SD**	**n**	**Mean**	**SD**	***P****
CGI-S total score	46	5.2	0.6	42	5.4	0.6	0.10
PANSS	46			42			
Total		85.5	17.3		90.9	17.6	0.15
Positive		21.9	5.1		23.4	4.6	0.17
Negative		20.5	5.8		20.5	6.3	0.99
General psychopathology		43.1	8.6		47.1	10.0	0.052
CDSS	46	1.8	3.3	42	2.3	4.2	0.57
GAF	46	35.4	6.0	42	35.2	6.5	0.88

*Independent *t* test.

CDSS indicates Calgary Depression Scale for Schizophrenia; CGI-S, Clinical Global Impression–Severity of Illness; GAF, Global Assessment of Functioning; PANSS, Positive and Negative Syndrome Scale.

We completely agree to the expert comment that more studies are necessary to evaluate effectiveness of risperidone and haloperidol combination in schizophrenia.

The average hospital stay in Taiwan is longer than that observed in Western countries. Perhaps this is due to the fact that in East Asian countries such as Japan and Taiwan, there has been almost no move to deinstitutionalization, which is ascribed to social, cultural, and political factors in these countries.[4] Furthermore, the Taiwan's National Health Insurance covers almost all the hospitalization fee (about US $100 daily).[5] Most of the participants agreed to stay in the hospital until the end of the study, even after they have improved. This could be considered a strength of the study. As inpatients, they were carefully monitored for symptoms, adverse effects, and medical adherence. A major difference in treatment between inpatients and outpatients is that medical adherence can be ascertained during hospitalization. If an outpatient has a good medical adherence, we assume that the conclusion of our study could be at least partially generalizable to him/her.

As shown in Table 1, the treatment groups were similar with respect to the baseline measures on the Clinical Global Impression–Severity, Positive and Negative Syndrome Scale and subscales, Calgary Depression Scale for Schizophrenia, and Global Assessment of Functioning.

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Comment on "Dose-Dependent Effects of Adjunctive Treatment With Aripiprazole on Hyperprolactinemia Induced by Risperidone in Female Patients With Schizophrenia"

To the Editors:

We read with great interest the article by Furukori et al,[1] which well described that adjunctive treatment with low-dosage aripiprazole lowers, dose-dependently, the elevated serum prolactin levels induced by risperidone treatment in female patients with schizophrenia. That effect occurs even when a low dosage (3 mg/d) of aripiprazole is used. It reaches a plateau at dosages greater than 6 mg/d.

However, sample collections for prolactin were only conducted 2 to 4 weeks after the dose escalation of aripiprazole. Therefore, the time course of changes of hyperprolactinemia, which occurs during 2 weeks, was not observed and therefore could not be evaluated. Ishitobi et al[2] reported that the early effect of adjunctive low-dosage aripiprazole (6 mg/d) in improving blonanserin-induced hyperprolactinemia was observed 12 hours after the initiation of aripiprazole and that normalization of serum prolactin levels was achieved rapidly within 5 days. The report of that case suggests that the period that is necessary to observe the effect of adjunctive aripiprazole in decreasing serum prolactin levels is shorter than a week.

It might be useful to assess the effect of adjunctive aripiprazole in decreasing serum prolactin levels during a short interval, with particular regard to worsening psychotic symptoms induced by adjunctive aripiprazole.

The study by Furukori et al would have been better executed and more useful if the sample collections for prolactin had also been conducted within a week to assess the time course of daily changes of hyperprolactinemia. Such an assessment might suggest a period that is sufficient to observe the effect of aripiprazole in decreasing serum prolactin levels at each dosage.

AUTHOR DISCLOSURE INFORMATION

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Reply to Comments by Dr Ishitobi et al

Reply:

The author appreciates the case report–based suggestion of Dr Ishitobi et al[1] that the concentration of prolactin decreases in less than 2 to 4 weeks because 5 additional days of an aripiprazole treatment was enough to do so in a female patient with blonanserin-induced hyperprolactinemia; however, taking blood samples at 1, 2, 3, 4, 5, 7, and 10 days for the purpose of prolactin monitoring is a potential ethical problem.

Because the pituitary gland is outside the blood-brain barrier, and prolactin response is dependent on dopamine D_2 blockers in the anterior pituitary, prolactin's response to antipsychotic agents partially depends on drug concentration in the plasma. When coadministered, aripiprazole may competitively inhibit risperidone binding to the dopamine D_2 receptor because it has a stronger affinity for the dopamine D_2 receptor compared to risperidone.[2,3] Moreover, aripiprazole's dopamine-antagonistic property decreases the concentration of prolactin. Therefore, the magnitude of the prolactin concentration decrease in the plasma is based on the dopamine D_2 receptor's binding affinity relationship between aripiprazole and another drug. When another drug has a stronger affinity for the dopamine D_2 receptor than aripiprazole, aripiprazole's effect on the decrease of the prolactin concentration should be small. The order of dopamine D_2 affinity of antipsychotic agents is as follows: blonanserin (K_i = 0.284) > aripiprazole (K_i = 0.988) > risperidone (K_i = 4.19).[4–6] In addition, the decreased time of the plasma prolactin concentration is related to the accumulation of aripiprazole in the peripheral plasma. The half-life (61 ± 31 hours for aripiprazole and 270 ± 44 hours for dehydroaripiprazole)[7] and apparent clearance determine the accumulation of aripiprazole. Since the time to reach plasma drug concentration at steady state needs the 5-time half-life period, it takes approximately 2 weeks to reach this steady state for aripiprazole and 8 weeks for dehydroaripiprazole. CYP2D6 and CYP3A4 metabolize aripiprazole.[8] A recent study found an interindividual variability in the aripiprazole clearance of the CYP2D6 genotype in Japanese patients.[9] Furthermore, when patients received other drugs that inhibited or induced these enzymes, their half-life or aripiprazole clearance was altered.

For these reasons, we cannot conclude that 5 additional days of aripiprazole treatment would have been enough to decrease the prolactin concentration induced by risperidone based on 1 blonanserin case study.[1] Additional studies are required to confirm the proposal of Ishitobi et al. However, our goal is not to decrease plasma prolactin concentrations but to improve prolactin-related adverse effects such as amenorrhea or loss of libido. Thus, a longer study (i.e., >3 menstrual cycles) is more appropriate to confirm the effect of an adjunctive aripiprazole treatment on hyperprolactinemia.

AUTHOR DISCLOSURE INFORMATION

The author declares no conflict of interest.

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