Letters to the Editor

Citalopram in the Maintenance Treatment of Major Depressive Disorder

Sir: I read with interest the article by Franchini and colleagues[1] on citalopram in the maintenance treatment of major depressive disorder (MDD). The study showed that no relapse was observed in the 4-month continuation period, during which patients were maintained on citalopram, 40 mg/day. However, during the 24-month maintenance phase, the dose was reduced to 20 mg/day, and 50% of patients had a new recurrence. The study did not have a placebo or a control arm. The results seem to contradict previous findings on the long-term efficacy of citalopram. The most likely cause for the high rate of recurrence in the report by Franchini et al. is the reduction in the dose of citalopram during the maintenance phase.

Previous studies have compared full-dose versus half-dose pharmacotherapy in the maintenance treatment of recurrent depression. Frank and colleagues[2] reported that superior prophylaxis can be achieved with full-dose compared with half-dose maintenance treatment strategy; the mean survival time for the full-dose subjects was 135.17 weeks compared with 74.94 weeks for the half-dose subjects.

In fact, several studies have assessed the efficacy of citalopram in the continuation and maintenance treatment of MDD. In a 24-week study of 20 mg of citalopram, 40 mg of citalopram, and placebo in the prevention of relapse of major depression, Montgomery and colleagues[3] found that both the citalopram 20- and 40-mg groups showed a significant advantage compared with placebo, both in relapses and in the survival analysis of time to relapse. Wade[4] evaluated the effectiveness of citalopram in the prevention of depression recurrence in a long-term, placebo-controlled, randomized withdrawal study. A total of 427 patients with recurrent MDD received 6 to 9 weeks of acute open treatment with citalopram, flexible dose 20–60 mg/day. Responders received 16 weeks of continuation treatment at their established effective dose. Patients who continued to respond (N = 269) were randomly assigned to 48 weeks or longer of double-blind treatment with either continued citalopram or placebo. The time to recurrence of depression was found to be significantly longer in patients treated with citalopram compared with placebo ($p < .0001$). Kylsner and coworkers[5] assessed the effectiveness of citalopram in the prevention of depression recurrence in 121 elderly patients. The study reported that the rate of depression recurrence was statistically significantly lower ($p < .0001$) in patients receiving citalopram maintenance therapy (16%, N = 19) compared with those receiving placebo (34%, N = 41). The difference was statistically significant at each dose level.

It is therefore suggested that the dose of antidepressant medication that leads to a satisfactory acute therapeutic response should be maintained during long-term treatment to prevent relapse or recurrence of depression.[6] It is surprising to see that the same group that showed twice as many relapses in paroxetine-treated patients when the dose was reduced to half compared with patients kept on the same dose of paroxetine[7] would then publish a study in which the dose was reduced to half during the maintenance phase without any control group. It is unclear what the authors would learn from a study that uses a substandard approach to the maintenance treatment of depression.

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Olanzapine, New-Onset Diabetes Mellitus, and Risk for Insulin Overdose

Sir: Olanzapine and clozapine are atypical antipsychotics with some similarities.[1] Kamran et al.[2] reported the first published case of new-onset diabetes mellitus associated with clozapine. Although causality is not established, a subsequent study of individuals with schizophrenia treated with clozapine for up to 5 years showed that 36.6% developed diabetes.[3] We report a case that illustrates a similar dilemma with olanzapine.

Case report. Mr. A, a white man with no prior personal or family history of diabetes or other medical conditions, was diagnosed with schizoaffective disorder at age 18 years; he was treated unsuccessfully with thioridazine, haloperidol, fluphenazine, molindone, thiothixene, and low-dose risperidone. He was on olanzapine, 10 mg/day, for the next 3 years with poor com-

pliance. Six weeks after compliance was strictly monitored while he was receiving 20 mg/day of olanzapine, he continued to have residual psychosis but could not tolerate the higher dose of olanzapine due to sedation. Therefore, quetiapine, 25 mg/day, was added for 6 days in addition to continuation of valproate and clonazepam; however, due to continued psychotic symptoms and increasing agitation, hospitalization was required. At admission, his fasting blood glucose level was 417 mg/dL (normal range, 75–119 mg/dL) and his hemoglobin A_{1c} proportion was 11% (normal range, < 6%). Glucose levels were returned to within the normal range with administration of insulin, 38 U q.a.m. and 24 U q.p.m. (70/30 mixture of isophane insulin suspension and regular insulin). His body weight at admission was 98 kg (218 lb), an increase of less than 2 kg (4 lb) over 3 years. Olanzapine was discontinued, and he was stabilized on quetiapine, 100 mg/day, and haloperidol, 10 mg/day.

In the 2 weeks after discharge, the patient's blood glucose levels were monitored and remained stable. However, the patient became increasingly psychotic and overdosed on insulin in a suicide attempt; the patient had 1 previous suicide attempt by drug overdose in 1998. The family reported that prior to the attempt he had voiced passive suicidal thoughts due to increased burden posed by his medical status. Although the exact amount of insulin injected is unknown, the family found a completely empty insulin vial by the patient's bedside; the first measurable blood glucose level was 40 mg/dL, and he remained difficult to arouse. After medical stabilization, quetiapine, 200 mg/day, and haloperidol, 10 mg/day, were started, along with insulin at prior doses. Over the next 2 months, insulin requirements decreased significantly (10 U q.a.m. and 8 U q.p.m.). Two months later, haloperidol and quetiapine were discontinued, and he was restarted on olanzapine, 30 mg/day, at another facility. During olanzapine treatment, insulin had to be increased (20 U q.a.m. and 20 U q.p.m.) to maintain a glucose level within the normal range. Due to breakthrough psychosis, olanzapine was discontinued and risperidone was initiated and titrated to 15 mg/day. The insulin dose had to be lowered and eventually discontinued due to hypoglycemia. The patient's glucose levels are currently within normal range.

As with other recent cases,[4] a subject with no known risk factors was incidentally diagnosed with diabetes while on olanzapine treatment. He did not have thyroid dysfunction or substance abuse. The possibility that other unknown variables (concomitant medications [especially valproate], genetic vulnerability, drug interactions, etc.) may have contributed to the onset of diabetes cannot be ruled out. However, there is good reason to suspect that diabetes was linked to olanzapine because it was diagnosed soon after monitored olanzapine therapy was begun and insulin requirements changed with olanzapine rechallenge and discontinuation. The role of quetiapine in the development of the diabetes cannot be ruled out, but seems less likely since the patient required less insulin during quetiapine treatment than during olanzapine treatment.

Although mechanisms are unknown, olanzapine may increase insulin resistance[5] in vulnerable patients. While olanzapine may be uniquely effective in some patients, it can potentially add the morbidity of diabetes and the need for compliance with insulin, particularly difficult in psychotic patients. Our patient's suicide attempt occurred while he was not taking olanzapine, and we are not implying that his suicide was a side effect of olanzapine. However, in patients already struggling with chronic mental illness, the added morbidity of diabetes mellitus may potentially lead to suicidality, as it did in this case. Further, while our patient may have overdosed on any medication, the availability of insulin magnified the dangerousness. In addition, discontinuation of olanzapine in patients taking insulin may potentially lead to severe hypoglycemia. This may have happened in our patient and can happen in noncompliant subjects. Clinicians must be acutely aware of these risks. The decision to stop or continue olanzapine is a difficult one. Changing to another antipsychotic carries the risk of psychosis flare but also, in some cases, the potential to reverse diabetes. Our case highlights the need to balance these factors. The potential link between diabetes and olanzapine needs further study.

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A Pilot Double-Blind, Dose-Comparison Study of Risperidone in Drug-Naive, First-Episode Schizophrenia

Sir: The efficacy and safety of risperidone in patients with first-episode schizophrenia have been demonstrated in open trials[1,2] and in controlled studies.[3] However, the optimal dosing of risperidone for this population remains controversial. In the open trial by Kopala et al.,[1] low doses of 2 to 4 mg/day (N = 11) were associated with better outcome than high doses of 5 to 8 mg/day (N = 11). Another small-scale open trial[2] also reported similar findings. In the double-blind study by Emsley et al.,[3] the mean final daily dose of risperidone was 6.1 mg (N = 99) and that of haloperidol, 5.6 mg (N = 84). In another study,[4] the mean daily dose was 4.2 mg for risperidone (N = 16) and 4.0 mg for haloperidol (N = 19). Recommendations for both low (2–4 mg/day)[5] and higher (4–8 mg/day)[6,7] doses are found in the literature. Of note, the previous trials are of limited value because they did not include random assignment to fixed doses of risperidone.

We conducted a pilot double-blind, fixed-dose, 6-week study to compare the effectiveness of 2 risperidone doses (3 mg/day and 6 mg/day) for first-episode DSM-IV schizophrenia. Twenty-four drug-naive and newly hospitalized patients entered the trial. They were 18 to 45 years old and physically healthy and had a minimum score of 60 on the Positive and Negative Syndrome Scale (PANSS).[8] After giving written informed consent, they were randomly assigned to either dose group. The dose was titrated to 3 or 6 mg/day over 1 week and kept unchanged during the following 5 weeks. One patient discontinued the trial

on day 5 due to physical illness. The other 23 patients (8 women/15 men, mean ± SD age = 30.8 ± 9.4 years) completed at least 1 assessment (on day 7) after randomization. Of the 23 patients, 20 finished the 42-day trial and the other 3 ended on days 14 or 28 due to side effects or uncooperativeness. An intent-to-treat analysis was carried out for the 23 subjects, with the last observation carried forward.

At baseline, the mean ± SD PANSS scores in the low-dose and the high-dose groups were 88.9 ± 11.6 (N = 11) and 89.1 ± 13.2 (N = 12), respectively. On day 7, only 1 patient, in the high-dose group, achieved response (20% or more reduction in PANSS score). On day 14, there were approximately half as many responders in the low-dose versus the high-dose group: 27.3% versus 50.0% (3/11 vs. 6/12). On day 28, however, almost 50% more patients in the low-dose versus the high-dose group responded: 72.7% versus 50.0% (8/11 vs. 6/12). On day 42, the response rates in the 2 groups converged: 63.6% versus 66.7% (7/11 vs. 8/12) for the low- and high-dose groups, respectively. By Kaplan-Meier estimates, the median time to first response was 28 days for both groups. The low-dose group tended to have fewer extrapyramidal side effects (assessed using the Extrapyramidal Symptom Rating Scale[9]) and other adverse events (assessed using the UKU Side Effect Rating Scale[10]). At endpoint, 3 low-dose patients and 6 high-dose patients received p.o. benztropine, and 5 low-dose patients and 4 high-dose patients used p.o. lorazepam. Throughout the trial, 2 patients in the low-dose group and 1 in the high-dose group received i.m. lorazepam for agitation. No other drugs were coadministered.

Since the introduction of risperidone, it has been found that rapid titration to 6 mg/day is inappropriate for many patients.[11] Several recent trials[12,13] suggest that the optimum dose for chronic schizophrenia is 4 mg/day. To date, there is a paucity of evidence concerning the effectiveness of risperidone doses of 2 to 4 mg/day in first-episode patients[1,2] or other populations.[14,15] Love et al.[15] reported that the inpatients they studied, regardless of diagnoses, were more likely to be discharged if they received 2 or 4 mg/day rather than 6 mg/day of risperidone. Caution should be exerted in interpreting the data, because it is possible that certain patients requiring higher doses might have been somewhat treatment resistant. Our recent study[14] demonstrated an individualized dosing strategy for acutely exacerbated schizophrenia. Nearly 60% of the patients tolerated the 6-mg target dose of risperidone. For the other 40% of patients, reducing doses to a mean of 3.6 ± 0.9 mg to relieve side effects still yielded efficacy.[14] However, those patients receiving lower doses also had fewer hospitalizations.[14] It is thus vital to confirm the effects of doses lower than 4 mg/day with well-designed studies enrolling homogeneous populations. To our knowledge, this pilot study is the first one utilizing a double-blind, fixed-dose design in first-episode patients to investigate the effectiveness of a low dose of risperidone. In summary, both low (3 mg/day) and high (6 mg/day) doses showed favorable efficacy. Certainly, it is too premature to draw any conclusion from so few subjects. Further studies with greater sample sizes and fixed-dose designs are warranted.

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