

Ziprasidone Alternative for Olanzapine-Induced Hyperglycemia

TO THE EDITOR: Among currently available atypical antipsychotic agents, clozapine and olanzapine are most often associated with clinically problematic weight gain and new-onset type 2 diabetes mellitus (1). Ziprasidone, a benzisothiazolylpiperazine, is a relatively new atypical antipsychotic that has been shown to be less likely to produce weight gain (2). We report on a patient with olanzapine-induced weight gain and type 2 diabetes whose blood glucose level returned to normal after he discontinued olanzapine and started treatment with ziprasidone.

Mr. A, a 42-year-old man with a 22-year history of paranoid schizophrenia, was admitted to a state psychiatric hospital in a psychotic condition. Three years earlier, after initiation of olanzapine at 20 mg/day, he had gained 15 lb and developed hyperglycemia. His fasting blood glucose level had fluctuated from 114 to 266 mg/dl for the past 2½ years. To control his diabetes, he was treated with dietary restrictions and metformin, 500 mg b.i.d.

Upon admission Mr. A's olanzapine regimen, 20 mg/day, was continued. After 8 weeks of inpatient treatment, his fasting blood glucose level remained at an abnormal level (150 mg/dl), despite dietary restrictions and metformin treatment, and his weight remained unchanged, at 215 lb (body mass index=30). Ziprasidone was initiated and titrated up to 120 mg/day while his olanzapine dose was tapered and then discontinued. Because of Mr. A's complaints of dizziness and sleepiness, his dose of ziprasidone was reduced to 100 mg/day.

Four days after he stopped taking olanzapine, Mr. A's fasting blood glucose level dropped to 73 mg/dl and remained within the normal range and stable (from 73 to 83 mg/dl) for three consecutive measurements over the next few days. Metformin therapy was tapered to 500 mg/day and then stopped. During 5 weeks of follow-up with ziprasidone therapy, Mr. A's psychotic symptoms substantially improved (his score on the Positive and Negative Syndrome Scale fell from 117 to 83), and he was discharged from the hospital with a fasting glucose blood level of 73 mg/dl and an unchanged weight.

We found 16 case reports describing new-onset diabetes associated with olanzapine treatment (1, 3). In some cases, hyperglycemia resolved after olanzapine was discontinued, and no further treatment was needed. However, the majority of the patients still required insulin therapy or oral hyperglycemic medication (1, 3).

It has been suggested that ziprasidone's unique combination of relatively low histamine H₁ affinity and potent serotonin 5-HT_{1A} agonist activity may be responsible for its lower propensity for weight gain (2) and, possibly, abnormalities in glucose-insulin homeostasis. This case suggests that ziprasidone may be a useful alternative for patients with antipsychotic-induced hyperglycemia.

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Ibuprofen and Psychotic Exacerbation

TO THE EDITOR: Nonsteroidal anti-inflammatory drugs may cause psychiatric symptoms in some patients (1, 2). This side effect has been recognized for ibuprofen, a prostaglandin synthesis inhibitor, and several other nonsteroidal anti-inflammatory drugs. Both de novo transient psychoses and emergence of a first psychotic episode have been described (3). To the best of our knowledge, there are no reports of psychotic exacerbation due to nonsteroidal anti-inflammatory drugs in schizophrenia patients maintained with antipsychotics. We recently encountered a patient with paranoid schizophrenia who developed a psychotic exacerbation after short-term treatment with ibuprofen for backache.

Mr. A, a 27-year-old man, had had DSM-IV paranoid schizophrenia for 4 years. He was originally treated with risperidone, 1-4 mg/day; he had been treated for the last 2 years with risperidone, 2 mg/day. He was in remission, without psychotic symptoms, and living at home.

Mr. A was instructed to take ibuprofen for backache, two 200-mg tablets each evening and an additional tablet in the morning. By noon, he was manifesting flight of ideas, pressure of speech, and difficulty concentrating. He felt very tired but was very agitated and unable to sleep. He also had feelings of grandeur and paranoid and bizarre delusions. He had no perceptual disturbances but had some insight into his mental condition. Mr. A ingested another tablet of ibuprofen, and after a short time, he experienced extreme aggravation. On emergency consultation with his psychiatrist, he stopped taking ibuprofen. Within 48 hours, his psychotic symptoms had disappeared.

This patient had a psychotic episode characterized by prominent delusions and manic features. The symptoms were linked in time to his ibuprofen exposure and cleared up completely soon after this treatment was stopped. There was no suggestion of other etiological factors, such as physical disease or drug or alcohol abuse. The patient's health was maintained with a stable dose of risperidone and no change in drug treatment.

A possible link between prostaglandins and psychotic symptoms has been suggested (4, 5). The molecular mechanisms involved in ibuprofen-induced mental status changes are unclear but may be related to a direct effect on brain activity or to an inhibitory effect on brain cyclooxygenase, prostaglandins, and neurotransmitters (6). This is the first report of which we are aware of a psychotic exacerbation in response to a nonsteroidal anti-inflammatory drug in a well-treated remitted schizophrenia patient. Health care professionals should be aware that nonsteroidal anti-inflammatory drug

treatment can be associated with psychotic exacerbation in some schizophrenia patients.

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Rhabdomyolysis With Simvastatin and Nefazodone

TO THE EDITOR: Pharmacotherapy for depression and hypercholesterolemia may result in potentially fatal drug-drug interactions involving the cytochrome P-450 (CYP-450) system. Hepatic hydroxymethyl glutaryl coenzyme (HMG-CoA) reductase inhibitors (simvastatin, atorvastatin, and lovastatin) are metabolized by the 3A4 isoenzyme, while ketoconazole, fluvoxamine, nefazodone, and even grapefruit juice inhibit it (1). In healthy adults, co-administration of simvastatin and nefazodone resulted in an approximately 20-fold increase in simvastatin and simvastatin acid (2). It is likely that the risk of rhabdomyolysis increases with high levels of HMG-CoA reductase activity in plasma (2). We report a case of such an interaction that followed the addition of nefazodone treatment for a patient receiving simvastatin. To our knowledge, this is only the second report of this probable interaction (3).

Mr. A, a 72-year-old Hispanic man with recurrent depression, anxiety, insulin-dependent diabetes mellitus, hypertension, and hyperlipidemia, was referred for severe depression and anxiety. His medications upon his visit to the psychiatrist were paroxetine, lorazepam, mirtazapine, risperidone, zolpidem, insulin, metformin, and simvastatin. Multiple previous antidepressant trials of sufficient dose and duration had failed to relieve his symptoms. His only significant laboratory test abnormality was a glucose level of 40 mg/dl; no subsequent glucose levels had been found to be lower than 74 mg/dl. The psychiatrist discontinued paroxetine, mirtazapine, lorazepam, and risperidone and initiated nefazodone, 100 mg b.i.d., clonazepam, and trazodone. Four weeks later, the nefazodone dose was increased to 300 mg at bedtime.

Two weeks later, Mr. A was admitted to the medical service with a 3-day history of generalized weakness, a cough, a fever, and a provisional diagnosis of viral syndrome. After admission, the results of laboratory tests included a creatinine kinase level of 10,555 U/liter, an aspartate aminotransferase level of 72 U/liter, a lactose

dehydrogenase level of 350 U/liter, and urine containing moderate blood, five to six red blood cells per high-power field, and one to two WBCs per high-power field. Mr. A's blood urea nitrogen, creatinine, and alanine aminotransferase levels remained within normal limits; his serum myoglobin level was not tested. Nefazodone was discontinued, Mr. A was hydrated intravenously, and 2 days later he was discharged with a creatinine kinase level of 3869 U/liter. He was feeling less weak and afebrile. One week later, his weakness had nearly resolved (his creatinine kinase level was 261 U/liter). He has continued taking simvastatin and venlafaxine without complications.

Nefazodone, a potent inhibitor of the CYP 3A4 system, should be used with caution in combination with 3A4 substrates, including simvastatin. We believe this patient's rhabdomyolysis was likely a result of this interaction. Although the rhabdomyolysis resolved with hydration and nefazodone discontinuation, renal failure may have occurred if clinical attention had not been sought (4). With an increasing rate of statin prescription (5) and nefazodone's possible association with liver failure (2), even more attention should be paid to possible complications related to these agents. Given this information, nefazodone may not be the best first-line antidepressant therapy for patients taking statins metabolized by the 3A4 system. When patients are given this drug combination, the symptoms of rhabdomyolysis should be carefully reviewed with them. Psychiatrists should be vigilant about reviewing medication lists for potentially serious drug interactions.

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Myocarditis With Quetiapine

TO THE EDITOR: To our knowledge, no case reports associating quetiapine treatment with myocarditis have yet been published, but two cases of cardiomyopathy with quetiapine administration are registered in the World Health Organization database (1). We present another case of myocarditis associated with quetiapine.

Mr. A, a 35-year-old man with paranoid schizophrenia, was admitted to a psychiatric hospital for the first time. Initially, he was medicated with benperidol and lorazepam, which led to the remission of acute psychosis. He developed extrapyramidal symptoms, and quetiapine, 800 mg/day, was introduced. On admission, a first-degree

atrioventricular block and an incomplete right bundle-bunch block were diagnosed. No history of heart disease or cardiac risk factors was found.

During Mr. A's first 2 months of monotherapy with quetiapine, 600 mg/day, mild eosinophilia (6% eosinophilia cells), thrombocytopenia (138 platelets/nl), and leukopenia (3.9 leukocytes/nl) developed. In the next 2 months, when Mr. A was still taking quetiapine without concomitant medications, a routine workup revealed high levels of creatinine kinase (107 U/liter), troponin (7.9 µg/liter), and C-reactive protein (75.9 mg/liter). In the last 4 days before the increase in his creatinine kinase level, Mr. A had a temperature of 37.8°C and reported nasal congestion with watery discharge, fatigue, and myalgia in the absence of chest pain.

Myocarditis was diagnosed on the basis of transient and ubiquitous ST wave elevation on ECG and elevation of cardiac enzyme levels. Nevertheless, myocardial infarction could not entirely be ruled out in the absence of catheterization. Mr. A's ECG showed normal global pump function and no pericardial effusion; long-term ECG revealed no arrhythmia.

Since the origin of Mr. A's myocarditis was unknown, quetiapine therapy was immediately withdrawn. He was treated with metoprolol, 10 mg/day, and ramipril, 2.5 mg/day. A decrease in Mr. A's levels of troponin and creatinine kinase was observed in the next 4 days, and he was considered cardiologically stable. Within 2 weeks after discontinuation of quetiapine, his eosinophilia, thrombocytopenia, and leukopenia resolved. Amisulpride was initiated without recurrence of psychiatric or cardiac symptoms.

For this patient, myocarditis may have been the result of a hypersensitive reaction to quetiapine. Evidence for this is 1) the appearance of eosinophilia, leukopenia, and thrombocytopenia at the beginning of treatment and their resolution after drug termination and 2) the influenza-like symptoms at the time of diagnosis in the absence of any other evidence of infection or hypersensitivity reaction. Furthermore, quetiapine is chemically similar to clozapine and olanzapine, and it is known that with treatment with these atypical antipsychotics, cardiac hypersensitivity reactions can occur (2–4). Additionally, patients who die of myocarditis associated with clozapine have had eosinophilic infiltrates in the heart muscle (5). However, in contrast to our patient, who developed myocarditis 4 months after treatment, most cases occurred within 6 weeks of clozapine treatment (5, 6).

An alternative explanation is that the patient's influenza-like symptoms reflected a viral etiology for myocarditis. However, this is unlikely, since cardiac symptoms usually begin 2 weeks after influenza symptoms appear. The fact that the patient's ECG was pathological before introduction of quetiapine means that it was unlikely to have contributed to myocarditis. Right bundle-bunch block is a common finding in young patients; the patient's atrioventricular heart block was neither aggravated with quetiapine treatment nor altered after its discontinuation.

Hypersensitivity reactions with quetiapine seem to be a parsimonious explanation for myocarditis in our patient. Clinicians should be alert to the potential appearance of this serious adverse effect when treating patients with quetiapine.

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Prolactin Elevation With Quetiapine

TO THE EDITOR: A recently published report by Peter Turrone, B.A. (Sp.H.), M.Sc., et al. (1) presented data indicating that the atypical antipsychotics risperidone, olanzapine, and clozapine produced serum prolactin elevations that were most prominent 1–5 hours after medication administration. With olanzapine and clozapine, serum prolactin levels had returned to baseline values by 12–24 hours. These findings have significant implications for understanding the binding properties of these compounds with dopamine D₂ receptors (2).

We completed a similar study to determine the effects of oral administration of quetiapine, another atypical antipsychotic, on serum prolactin levels in young first-episode patients with a schizophrenia spectrum disorder.

Four patients (two men and two women, mean age=21 years) participated. Each patient gave written informed consent. They were clinically stable with quetiapine monotherapy. All of the patients had been treated with quetiapine for more than 6 months. On the day of testing, they were instructed to withhold their morning dose of quetiapine and to come for testing at noon. Blood samples were drawn before the patients took their full daily dose (two patients were taking 700 mg/day, and two were taking 800 mg/day) and every 30 minutes thereafter for 3 hours.

Baseline serum prolactin levels were not abnormal (<10 ng/ml). However, all four patients had significant serum prolactin elevations within 90 minutes of drug administration. Two patients had peak prolactin levels (115 ng/ml and 120 ng/ml) occurring 60 minutes after they took the dose, while for the other two participants, peak levels (80 ng/ml and 84 ng/ml) occurred 90 minutes later. In all patients, serum prolactin levels declined from the peak value over the remaining observation times. Three hours after administration, serum prolactin levels (30 ng/ml to 60 ng/ml) were still above baseline levels in all four patients.

The magnitude of the prolactin elevations was considerably greater than what has been previously reported for risperidone, olanzapine, and clozapine (1). We administered the full daily dose of quetiapine to patients who had rou-

tinely received the drug in divided doses. Hence, the predicted serum prolactin elevations under the divided-dose regime would have been considerably lower than reported here and likely more comparable to the data for other atypical antidepressants.

These results indicate that oral administration of quetiapine was associated with a marked but transient increase in serum prolactin levels. The results support the view that a relatively rapid dissociation from dopamine receptors is central to the mechanism of action of atypical antipsychotics (2).

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Pregnancy Outcomes in Schizophrenia

TO THE EDITOR: The title of the intriguing report by Gideon Koren, M.D., F.A.B.M.T., F.R.C.P.C., and colleagues (1) unfortunately implies that the authors directly studied women taking atypical antipsychotics during pregnancy and the drugs' association with neural tube defects. The authors evaluated the folate status of men and women with schizophrenia who received atypical antipsychotics and found lower serum folate levels, lower dietary folate intake, and a higher risk of obesity in a subgroup of subjects. The authors posited that infants of women with schizophrenia are at a greater risk for neural tube defects because of both maternal obesity and low folate intake. They suggested that women with schizophrenia are a high-risk population and that high-dose folate supplementation should be considered.

However, the number of women in the overall study group (21 of 70) was small. The number of women in the folate dietary intake subgroup (total N=37) was not provided. The ages of the women were not given, although the study group included subjects aged through 73 years. Women's folate intake and absorption may not be the same across the lifespan.

Disturbances of folate metabolism may be related directly to schizophrenia. Susser et al. (2) found that a folate-sensitive defect in homocysteine metabolism contributes to the development of schizophrenia. Hyperhomocysteinemia in pregnant women increases the risk of neural tube defects; folate treatment may normalize homocysteine metabolism, thus reducing the risk (3). Studies of nutritional status in pregnancy have found that mothers of fetuses affected with neural tube defects have normal or mildly low levels of folate (4). Not all of the known risks for neural tube defects, such as maternal age, birth order, or febrile illness, operate through folate-dependent mechanisms.

The authors' important findings raise questions regarding whether women with schizophrenia should complete a dietary history of folate intake or have serum folate levels assessed. It is also unclear if they should have B₁₂ levels checked, since deficiency is an independent risk factor for neural tube defects (4).

The authors also noted that the risks of taking atypical antipsychotics, such as weight gain and diabetes, require special consideration for use in women of childbearing age. Interventions to achieve weight reduction in women with schizophrenia warrant study. This report raises numerous questions that compel further evaluation of nutritional variables related to pregnancy outcome for women with schizophrenia. Studies that examine risk for neural tube defects in these women's infants and whether folate treatment lowers this risk are needed. Gestational risks related to schizophrenia must be differentiated from those of the drugs used to treat it.

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Dr. Koren Replies

TO THE EDITOR: I thank Dr. Freeman and colleagues for their thoughtful remarks. Our investigation into the folate status of women with schizophrenia emanated from the case of a woman taking olanzapine who experienced a very large weight gain and whose fetus had a large neural tube defect. Since the publication of our study of schizophrenia patients, Motherisk has initiated a prospective follow-up study of women with schizophrenia regarding folate status and other obstetric risks. Every woman with schizophrenia counseled by us, either while planning a pregnancy or while already pregnant, is offered a measurement of folate levels, counseling on supplementation, and repeated measurements to verify compliance, plus a screening for neural tube defects. The idea of Dr. Freeman and colleagues of investigating the dietary status of women is logical and important since other critical nutrients and micronutrients may also be lacking.

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