

Letters to the Editor

Inaccurate Information on Quetiapine

Sir: I would like to correct several errors in the recent *ACADEMIC HIGHLIGHTS* report on atypical antipsychotics¹ with respect to quetiapine fumarate (Seroquel):

- (1) The reference cited for the "long-term study" (Cantillon and Arvanitis²) is incorrect. The correct reference should be Arvanitis and Rak.³
- (2) While this was a 52-week trial on efficacy, safety, and tolerability of quetiapine in elderly subjects with psychotic disorders, the data actually presented at the American Psychiatric Association meeting were from a 12-week interim analysis of this study. No long-term data were presented.
- (3) The patient numbers referred to in the article, i.e., 12 patients completed 16 weeks of treatment and 6 patients completed a year of treatment, are incorrect. The correct patients numbers to cite from the 12-week interim analysis are as follows: 151 patients were enrolled and received trial medication, 36 (24%) patients withdrew from the trial: 13 (9%) had adverse events, 12 (8%) refused to continue or were lost to follow-up, 9 (6%) withdrew because of lack of effect, and 2 (1%) because of protocol noncompliance.
- (4) Citing the frequency of side effects from this study as being "quite high" is misleading, and the numbers presented were totally inaccurate. The correct numbers for the side effects mentioned should be: agitation 11% (not 53% as cited), somnolence 32% (not 40% as cited), and constipation 8% (not 27% as cited).

Quetiapine is an atypical antipsychotic agent that is effective against both the positive and negative symptoms of schizophrenia, with an excellent tolerability and safety profile including no treatment-emergent extrapyramidal side effects or increases in serum prolactin levels across the entire antipsychotic dose range. It is this profile that makes quetiapine an attractive alternative to standard agents, particularly in elderly patients who are especially sensitive and cannot tolerate the motor side effects often associated with antipsychotic therapy. It is for these patients I would like to set the quetiapine record straight so that it appropriately reflects the enthusiasm that has been shown in the psychiatric community for this beneficial drug.

REFERENCES

1. Masand PS. Atypical agents in nonschizophrenic disorders, pp 322–324. In: Marder SR, chairperson. *Atypical Antipsychotic Agents in the Treatment of Schizophrenia and Other Psychiatric Disorders, Part II: Special Considerations [ACADEMIC HIGHLIGHTS]*. *J Clin Psychiatry* 1998;59:322–328
2. Cantillon M, Arvanitis LA. Efficacy, safety, and tolerability of quetiapine in elderly subjects with psychotic disorders. In: *New Research Program and Abstracts of the 150th Annual Meeting of the American Psychiatric Association*; May 20, 1997; San Diego, Calif. Abstract NR231:130

3. Arvanitis LA, Rak IW. The long-term efficacy and safety of quetiapine. In: *New Research Program and Abstracts of the 150th Annual Meeting of the American Psychiatric Association*; May 20, 1997; San Diego, Calif. Abstract NR230:130

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Dr. Masand Replies

Sir: The data on quetiapine reported in the *ACADEMIC HIGHLIGHTS* in the June 1998 issue were derived from my presentation at a 1997 American Psychiatric Association (APA) symposium. These were taken from the poster presented by Apter et al.¹ at the 1996 American College of Neuropsychopharmacology meeting. At the time I prepared my presentation for the 1997 APA conference, the Apter et al. report on quetiapine in the elderly was the only one available. What has confused Dr. Goldstein is that Apter et al. were not cited in the *ACADEMIC HIGHLIGHTS*; instead, and erroneously, the citation provided for the quetiapine data was Cantillon and Arvanitis, 1997.² I welcome the more recent information on the use of quetiapine in elderly patients provided by Dr. Goldstein and apologize for the mix-up in the citation.

REFERENCES

1. Apter JT, Allen LA, Arvanitis LA, et al. Seroquel experience in the elderly. Presented at the 35th annual meeting of the American College of Neuropsychopharmacology, December 9–13, 1996; San Juan, Puerto Rico. *Scientific Abstracts*, p 261
2. Cantillon M, Arvanitis LA. Efficacy, safety, and tolerability of quetiapine in elderly subjects with psychotic disorders. In: *New Research Program and Abstracts of the 150th Annual Meeting of the American Psychiatric Association*; May 20, 1997; San Diego, Calif. Abstract NR231:130

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Hyperglycemia Associated With Olanzapine

Sir: Olanzapine, a thienobenzodiazepine, is an atypical antipsychotic agent similar to clozapine, risperidone, and quetiapine in that it selectively binds to serotonin receptors. It also has an affinity for the D₂, D₄, D₁, muscarinic, α_1 -adrenergic, and H₁ histaminic receptors.¹ Olanzapine is well tolerated and has a safety profile associated with a low incidence of extrapyramidal movements and agranulocytosis.¹

Adverse events commonly reported with olanzapine include somnolence, agitation, asthenia, nervousness, dizziness, and weight gain.¹ Among the 2500 primary clinical trial participants, hyperglycemia and diabetes mellitus were found to occur

infrequently (1/100 to 1/1000).² We describe a patient who developed hyperglycemia 6 weeks after beginning olanzapine therapy, which resolved upon discontinuation of the drug and reappeared after rechallenge.

Case report. Mr. A, a 32-year-old mentally retarded African American man, had a 4-year history of personality disorder and psychotic disorder characterized by stress-induced hallucinations. He was started on olanzapine, 10 mg q.h.s. Mr. A also had a history of polysubstance and alcohol abuse. Significant medical findings included obesity (height = 67", weight = 99.5 kg), history of borderline hypertension (medication-free), chronic active hepatitis C, chronic allergic rhinitis, and positive tuberculin skin test.

Mr. A did not have a prior personal or family history of diabetes mellitus or glucose intolerance, although hypertension, race, and obesity could predispose him to these conditions. Prior to beginning olanzapine therapy, Mr. A was taking the following medications: fluphenazine, 15 mg/day; benztropine, 4 mg/day; and beclomethasone nasal spray, 1 spray in each nostril b.i.d. (168 µg/day). After Mr. A started olanzapine therapy, fluphenazine was decreased to 10 mg q.h.s. for 7 days and then to 5 mg q.h.s. for 7 days before being discontinued. Benztropine was tapered down to 1 mg/day and subsequently discontinued because Mr. A did not have extrapyramidal symptoms during olanzapine therapy. Olanzapine was started at 10 mg q.h.s. with subsequent titration to 15 mg q.h.s. at 3 weeks and 20 mg q.h.s. at 9 weeks.

After 6 weeks of olanzapine therapy, a routine chemistry panel revealed an elevated blood glucose level of 290 mg/dL. This was to our knowledge the first incidence of hyperglycemia in this patient, as previous fasting blood glucose levels were less than 100 mg/dL. Subsequent fasting blood sugar levels over the next month ranged from 300 to 402 mg/dL, and hemoglobin A_{1c} was 13.8% (normal < 6.5%). Initially, Mr. A was placed on a sliding scale insulin regimen. Blood glucose levels were not controlled on this regimen; therefore, beclomethasone nasal spray was stopped, olanzapine was decreased to 15 mg q.h.s., and NPH human insulin 15 units SQ each morning was started. Daily Accucheck (fingerstick) readings continued to be elevated, which necessitated the titration of NPH human insulin to 32 units SQ each morning and 12 units SQ each day at 4 p.m. Olanzapine was discontinued after 13 weeks of therapy, and Mr. A began a trial of chlorpromazine at an initial dose of 45 mg/day. Blood glucose levels returned to normal approximately 2 weeks after olanzapine was stopped and averaged 103 mg/dL over the next several months, thus permitting discontinuation of insulin.

Mr. A was rechallenged with olanzapine, 5 mg q.h.s., 8 months after his first trial. Rechallenge resulted in hyperglycemic episodes once again. Eight days after olanzapine was restarted, Mr. A's fasting blood glucose level was 254 mg/dL. Insulin was not prescribed at that time. Olanzapine was stopped, and chlorpromazine was titrated up to 150 mg/day. Blood glucose levels returned to normal several weeks after discontinuation of olanzapine, and daily Accuchecks were discontinued.

This case is significant because the hyperglycemia required insulin therapy, resolved after olanzapine was stopped, and recurred upon rechallenge. There did not seem to be a dose-effect relationship in this patient, since fasting blood glucose levels were similar with olanzapine dosages of 15 mg q.h.s. and 20 mg q.h.s.

High-dose systemic glucocorticoids have been shown to induce hyperglycemia in some patients; however, Mr. A was using a topical glucocorticoid formulation, nasal beclomethasone.³ Topical glucocorticoids have not been associated with signifi-

cant alterations in blood glucose concentrations.³ In this case, Mr. A stopped using beclomethasone several weeks before the first trial of olanzapine was discontinued, and his blood glucose levels remained elevated.

As noted previously, Mr. A had chronic active hepatitis C. Glucose intolerance has been noted in patients with liver disease; however, Mr. A had no prior episodes of hyperglycemia.⁴ Given his medical history, it is possible that Mr. A had unrecognized type 2 diabetes.

Induction of hyperglycemia has been reported with the traditional antipsychotics chlorpromazine, loxapine, and amoxapine.^{5,6} Several authors have proposed hypotheses for antipsychotic-induced hyperglycemia; however, conclusive evidence is still lacking.⁵⁻⁸ It is interesting to note that clozapine has been associated with hyperglycemia in 7 separate case reports, 6 of which involved African American individuals.⁹⁻¹² Most of the affected patients developed hyperglycemia 5 to 8 weeks after starting clozapine, with normalization of blood glucose levels occurring after discontinuation of clozapine.^{9,10} Two patients were rechallenged with clozapine and experienced hyperglycemic episodes after 3 to 10 days of therapy.^{9,11} On the basis of these findings, this case report suggests that the induction of hyperglycemia by clozapine and olanzapine occurs in a similar temporal pattern with initial therapy as well as rechallenge therapy.

Since this letter was accepted for publication, 2 olanzapine- and 4 clozapine-associated diabetes cases have been published.¹³ There are several similarities between the current case and the olanzapine cases of Wirshing and associates. Although only 1 case patient had a positive family history for diabetes, to date, all of the olanzapine-induced hyperglycemia cases have occurred in obese, male patients. In addition, 2 of the 3 olanzapine patients were African Americans. This is suggestive that patients typically at risk for insulin resistance based on race or obesity may be at greater risk for olanzapine-induced hyperglycemia. The olanzapine was not discontinued in the patients of Wirshing and colleagues, but rather their hyperglycemia was controlled with medication; therefore, it is not known whether the drug-induced diabetes would have resolved upon olanzapine discontinuation as was observed in the current case. Further studies are needed to determine the effect of olanzapine and other atypical agents on glycemic control.

REFERENCES

1. Beasley CM, Tollefson G, Tran P, et al. Olanzapine versus placebo and haloperidol: acute phase results of the North American double-blind olanzapine trial. *Neuropsychopharmacology* 1996;14:111-123
2. Zyprexa (olanzapine). Physicians' Desk Reference. Montvale, NJ: Medical Economics; 1998:1512-1518
3. Kruszynska YT, Greenstone M, Home PD, et al. Effect of high dose inhaled beclomethasone dipropionate on carbohydrate and lipid metabolism in normal subjects. *Thorax* 1987;42:881-884
4. Fraser GM, Harman I, Meller N, et al. Diabetes mellitus is associated with chronic hepatitis C but not chronic hepatitis B infection. *Isr J Med Sci* 1996;32:526-530
5. Proakis AG, Mennear JH, Miya TS, et al. Phenothiazine-induced hyperglycemia: relation to CNS and adrenal effects. *Proc Soc Exp Biol Med* 1971;137:1385-1388
6. Tollefson G, Lesar T. Nonketotic hyperglycemia associated with loxapine and amoxapine: case report. *J Clin Psychiatry* 1983;44:347-348
7. Wannarka GL, Fletcher HP, Schnell RC. Variations of chlorpromazine related isoterics on the glycemic response in mice. *Gen Pharmacol* 1979;10:169-172
8. Krausz Y, Wollheim CB, Siegel E, et al. Possible role of calmodulin in insulin release: studies with trifluoperazine in rat pancreatic islets. *J Clin Invest* 1980;66:603-607

9. Popli AP, Konicki PE, Jurjus GJ, et al. Clozapine and associated diabetes mellitus. *J Clin Psychiatry* 1997;58:108–111
10. Kamran A, Doraiswamy PM, Jane JL, et al. Severe hyperglycemia associated with high doses of clozapine [letter]. *Am J Psychiatry* 1994;151:1395
11. Koval MS, Rames LJ, Christie S. Diabetic ketoacidosis associated with clozapine treatment [letter]. *Am J Psychiatry* 1994;151:1520–1521
12. Peterson GA, Byrd SL. Diabetic ketoacidosis from clozapine and lithium cotreatment. *Am J Psychiatry* 1996;153:737–738
13. Wirshing DA, Spellberg BJ, Erhart SM, et al. Novel antipsychotics and new onset diabetes. *Biol Psychiatry* 1998;44(8):778–783

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St. John's Wort and Hypomania

Sir: The herbal remedy St. John's wort (*Hypericum perforatum*) has gained increasing attention as a treatment for depression. Several European studies support the efficacy of St. John's wort in treating mild-to-moderate depression¹; however, interpretation of these findings has been limited by methodological problems in the existing research.² The mechanism of action of St. John's wort is unknown, although serotonin reuptake inhibition has been suggested as a basis for its mood-elevating effects.^{3,4} One of the herb's attractions has been its relative safety and tolerability compared with standard antidepressant therapy.¹ I report a case of St. John's wort inducing a hypomanic mixed state in a patient who suffered from panic disorder and depression.

Case report. Ms. A, a 47-year-old woman, presented with an 8-year history of nocturnal panic attacks. She described awakening each night sweating, anxious, tachycardic, and feeling panicked. As her symptoms worsened, she noted onset of depressive symptoms, including feelings of sadness, worthlessness, decreased concentration, poor memory, and periodic suicidal thoughts. She obtained relief from her panic and depressive symptoms with alprazolam, 0.25 mg/day, and paroxetine, 20 mg/day. At the time of initial assessment, Ms. A met DSM-IV criteria for panic disorder and unipolar major depression.

Ms. A continued with complete relief of her symptoms on paroxetine treatment for several months, but complained of fatigue and anorgasmia. Her medication was switched to sertraline, which was titrated to 75 mg/day. She noted feeling "a thousand times better" on sertraline treatment, continued to have relief from her panic symptoms, and no longer felt fatigued. However, her sexual side effects persisted. After several months, Ms. A began exhibiting significant irritability and insomnia. Sertraline was decreased to 50 mg, and the new symptoms resolved.

Ultimately, Ms. A discontinued sertraline because of sexual side effects. After waiting a week, and allowing the side effects to resolve, she started taking St. John's wort, a 0.1% tincture solution that she purchased at a health food store. She followed the instructions on the label, but after 10 days noticed racing and distorted thoughts, increased irritability, hostility, aggressive behavior, and decreased need for sleep. She described "feeling speedy" and began driving aggressively; she later described her state as one of "radical agitation." Ms. A discontinued the St. John's wort and noted complete resolution of her symptoms in 2 days.

Although she lacked a prior history of mania or hypomania, Ms. A demonstrated a vulnerability to activation while taking moderate doses of sertraline. The activation resolved completely during the sertraline washout and recurred 10 days after initiation of St. John's wort. Thus, there is a clear temporal association between the onset of hypomanic symptoms and the use of St. John's wort. It is unlikely that sertraline withdrawal or a sertraline–St. John's wort interaction accounted for the second hypomanic episode, given the washout period and the resolution of Ms. A's symptoms in the interval.⁵

This case suggests that St. John's wort can cause one of the complications associated with antidepressants, namely induction of hypomania and mixed states.⁶ As many patients attempt to seek alternative treatments for their depression, clinicians should caution patients that herbal remedies are not without potentially serious side effects. Indeed, given that St. John's wort is readily available in health food stores and currently unregulated in this country, this case raises the question as to what further investigation is needed to determine the effects of herbal remedies on mental health and what controls, if any, should regulate their use.

REFERENCES

1. Linde K, Ramirez G, Mulrow CD, et al. St. John's wort for depression: an overview and meta-analysis of randomised clinical trials. *BMJ* 1996;313:253–258
2. De Smet PA, Nolen WA. St. John's wort as an antidepressant. *BMJ* 1996;313:241–242
3. Riley ME. St. John's wort. *Rev Nat Prod*. Nov 1997:1–3
4. Chavez ML, Chavez PI. Saint John's wort. *Hosp Pharm* 1997;32:1621–1632
5. Dilsaver SC, Greden JF. Antidepressant withdrawal phenomena. *Biol Psychiatry* 1984;19:237–256
6. Wehr TA, Goodwin FK. Can antidepressants cause mania and worsen the course of affective illness? *Am J Psychiatry* 1987;144:1403–1411

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Edema Associated With Addition of Risperidone to Valproate Treatment

Sir: We report a second case¹ of acute generalized edema following the addition of risperidone to a regimen involving valproate.

Case report. Ms. A, a 40-year-old inpatient with severe and refractory schizoaffective disorder complicated by violence and noncompliance with treatment, had exogenous obesity but no history of edema or of heart failure, hepatic cirrhosis, hypoproteinemia, nephrosis, hypothyroidism, or vascular occlusive disease. She had taken valproate (90–110 µg/mL) and high doses of fluphenazine for over 3 years and had taken clonazepam for 6 months.

Risperidone, titrated to 10 mg/day over 2 months, was added to address an increase in psychosis and agitation. By the end of this 2-month period, Ms. A had developed marked edema in the lower extremities and moderate edema in the upper extremities and face. Physical examination including measurement of orthostatic vital signs, electrolytes, renal function, liver function including serum albumin, thyroid function, and valproate levels, pregnancy test, chest radiographs, echocardiogram, and pelvic ultrasound revealed no explanation for the edema. Furosemide, at doses of up to 160 mg/day, only partly reduced the edema,

despite causing symptomatic intravascular volume depletion. The edema remained stable after discontinuing diuretics and lowering the risperidone dose to 6 mg/day, and resolved entirely within 1 week of reducing the dose to 2 mg/day. Ms. A's condition quickly deteriorated, though, prompting a return of the risperidone dosage to 8 mg/day. One week later, the edema had returned, accompanied by a 15-lb (6.5-kg) weight gain. Risperidone was discontinued over the following week, and the edema resolved without diuretics.

Risperidone thus appeared to cause generalized (primarily dependent) edema in a dose-related fashion. As in the previously reported case,¹ edema was noted when risperidone was added to a regimen including valproate and a benzodiazepine. We examined the other 10 inpatients at our facility taking both risperidone (2–14 mg/day) and valproate and found no peripheral edema.

We encourage others to be alert to this complication of risperidone, which perhaps only occurs when coadministered with valproate and/or benzodiazepines.

REFERENCE

1. Baldassano CF, Ghaemi SN. Generalized edema with risperidone: divalproex sodium treatment [letter]. *J Clin Psychiatry* 1996;57:422

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**Nefazodone for Mood Disorder
 Associated With Epilepsy**

Sir: Nefazodone, a newer antidepressant with a dual action on the serotonin system, is effective in major depression,¹ comorbid anxiety and depression,² and possibly other conditions such as panic disorder. It is a relatively safe drug with a favorable side effect profile,³ and its favorable effect on sleep has been documented.⁴ The present case is the first reported that demonstrates another possible indication of nefazodone: mood disorder associated with a general medical condition, in this case, seizure.

Case report. Mr. A, a 23-year-old man, was referred to me by his neurologist for "behavioral problems." Since childhood, he had been treated with various medications for epilepsy, mostly of the grand mal type, and complex partial seizure, most likely beginning in the right temporal region with secondary generalization. He suffered from viral encephalitis at 2 years of age. At the time he was referred to me, his seizure disorder was well controlled with gabapentin, 1200 mg/day, and he had had his last seizure 11 months before his psychiatric evaluation. His psychiatric history was significant for treatment for hyperactivity with methylphenidate and thioridazine during childhood. He had never been treated for depression.

Mr. A reported being depressed and irritable and had recently slept only 3 to 4 hours per night. He denied any suicidal or homicidal ideation; however, he reported "giving up hope." His mood alternated from irritable and "hyper" to lethargic and sleepy. He was unable to make decisions. During the evaluation, he paced and was dysphoric, jumpy, tense, and nervous.

Mr. A was started on nefazodone, 100 mg at night. Within 1 week, he reported significant improvement in that he was able to sleep 6 to 7 hours per night and was much calmer. He denied side effects. The improvement was independently confirmed by his mother. He continued to do well 1 month later, still taking nefazodone, 100 mg at night, and gabapentin, 1200 mg/day. His depression gradually improved. Two months later, Mr. A reported increased irritability and nervousness. Nefazodone was increased to 300 mg/day, and he reportedly calmed down. He found a new job and started to date. Six months later, he was calm and euthymic and denied irritability, anxiety, sleep difficulties, or side effects.

The prompt effectiveness of antidepressants for the treatment of mood disorder associated with epilepsy has been described recently.⁵ Depressed mood and insomnia are symptoms of the pleomorphic and intermittent interictal dysphoric disorder. Interictal dysphoric disorder often may become manifest after seizures are suppressed by antiepileptic medication, as documented in this case. Antidepressants tend to be effective within days, at a modest dose, for the full range of the symptoms of interictal dysphoric disorder, not merely for depressive symptoms.

It is interesting that nefazodone, like other antidepressants,⁵ may be effective for the interictal mood disorder that is a common finding in chronic epilepsy. Promptly providing good sleep for a patient with interictal dysphoria seems to be important. A low dose of nefazodone swiftly improved Mr. A's sleep, decreased his tension, and gradually improved his mood. Nefazodone, with its favorable effect on sleep,⁴ might be a useful option in the treatment of patients with mood disorder associated with other medical conditions such as seizure, especially when sleep disturbance is a prominent part of symptomatology.

REFERENCES

1. Marcus RN, Mendels J. Nefazodone in the treatment of severe, melancholic, and recurrent depression. *J Clin Psychiatry* 1996;57(suppl 2):19–23
2. Zajecka JM. The effect of nefazodone on comorbid anxiety symptoms associated with depression: experience in family practice and psychiatric outpatient settings. *J Clin Psychiatry* 1996;57(suppl 2):10–14
3. Robinson DS, Roberts DL, Smith JM, et al. The safety profile of nefazodone. *J Clin Psychiatry* 1996; 57(suppl 2):31–38
4. Armitage R, Rush AJ, Trivedi M, et al. The effects of nefazodone on sleep architecture in depression. *Neuropsychopharmacology* 1994;10:123–127
5. Blumer D. Antidepressant and double antidepressant treatment for the affective disorder of epilepsy. *J Clin Psychiatry* 1997;58:3–11

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