

## Quetiapine: Another Drug With Potential for Misuse? A Case Report

**Sir:** The introduction of atypical antipsychotics in the early 1990s opened a new era in the management of schizophrenia and bipolar disorders.<sup>1</sup> Although not officially approved, some of these agents have lately been tried for the adjunctive treatment of substance abuse.<sup>2-5</sup>

Several studies suggest that quetiapine may reduce craving in alcohol-dependent individuals.<sup>3,5-7</sup> To date, there are no reports of quetiapine misuse in this context. Herein, we report a case of quetiapine misuse in a patient with alcohol and benzodiazepine dependence.

**Case report.** Mr. A, a 48-year-old man, was admitted to our clinic in 2006 for treatment of alcohol and benzodiazepine abuse (DSM-IV criteria). The patient was first prescribed benzodiazepines and antidepressants at the age of 23 years when apparently he had been diagnosed as suffering from generalized anxiety disorder. Over the next 10 years, the patient gradually developed tolerance to bromazepam, and the dosage slowly escalated to 12 to 24 mg/day. After Mr. A had a depressive reaction to adverse life events, benzodiazepine abuse was complicated with heavy alcohol drinking. The patient soon developed tolerance to alcohol, too, and eventually consumed more than a bottle of whiskey every evening. In a short period, a vicious circle developed of alcohol and high doses of bromazepam being successively abused. This pattern of abuse lasted for almost 15 years, until he was first admitted to our clinic, a year ago, for a 1-month alcohol detoxification.

At discharge, the patient was symptom-free and abstinent from alcohol and bromazepam; quetiapine 100 mg/day, clonazepam 2 mg/day, and vitamins had been prescribed at the beginning of the detoxification program, and he was referred for follow-up to the hospital's specialized outpatient drug addiction service. Clonazepam was prescribed as an anxiolytic for its long half-life and lower potential for abuse, and quetiapine for its purported anti-craving properties. Within 3 months, the patient started abusing clonazepam (8 mg/day) and alcohol with the same pattern as before and therefore had to be readmitted to hospital. However, soon after his second discharge from the hospital, he relapsed into alcohol abuse and started taking quetiapine, either alone or in combination with clonazepam, in ever-increasing doses, which reached 1000 mg/day over a couple of weeks. It should be noted that quetiapine can be obtained without a special prescription in Greece. He mentioned that clonazepam alone could not ease the symptoms of anxiety, expansive mood, irritability, confusion, and dizziness that alcohol consumption produced and that the combination of high doses of quetiapine and clonazepam produced the "perfect result" for him. He also felt that quetiapine augmented clonazepam's sedative action.

At the time of the start of his present hospitalization, the patient was taking 1000 mg of quetiapine and 16 mg of clonazepam per day. The pattern of abuse he had developed consisted of drinking a bottle of whiskey every second evening followed by quetiapine and clonazepam intake, which was repeated on the next day without alcohol consumption. It is noteworthy that the patient still abused these drugs when alcohol was not accessible to him and that he often preferred this combination to alcohol. Moreover, although sometimes he could manage to remain abstinent from alcohol during short time periods, he could not refrain from taking quetiapine and clonazepam. According to the

patient's report, while taking the above combination of drugs, he was feeling well and could adequately function in his everyday life. Conversely, upon discontinuation he manifested tremor, anxiety, sleep disturbance, and irritability, as well as significant impairment in his family and professional life.

Sporadic quetiapine misuse has been reported in special populations during the last couple of years.<sup>8-11</sup> Actually, a "street" value has been allotted to quetiapine on the black market, where it is preferably used for its sedative effect,<sup>12</sup> like benzodiazepines are commonly abused. This is the first case in the literature describing simultaneous abuse of alcohol, a benzodiazepine, and quetiapine. Furthermore, the present case illustrates the clinical difficulties encountered with substance-abusing patients when it is often impossible to distinguish between the true therapeutic effect of drugs taken by patients, their intention to self-medicate for anxiety and withdrawal symptoms, and the drug's potential primary rewarding effect.

Although the underlying mechanism for such a misuse is not known, some suggestions can be advanced. It has been established that the rewarding properties of addictive drugs depend largely on their capacity to increase mesolimbic dopamine<sup>13,14</sup>; also, typical high-potency antipsychotics, which are potent blockers of dopamine release in the mesocorticolimbic system, have been reported to either increase or decrease substance use.<sup>15,16</sup> On the other hand, atypical antipsychotics with significantly lower dopamine blockade potential, such as quetiapine, might be more beneficial for the treatment of substance abuse.<sup>2-5</sup> Therefore, although, in principle, quetiapine at regular doses may transiently block the dopaminergic reward pathway in the limbic system, at high doses it may exert a more potent dopamine antagonistic effect, promoting a self-feeding pattern of substance misuse instead.<sup>17,18</sup> Another putative mechanism of action is related to the probably dose-dependent sedative properties of quetiapine due to histamine H<sub>1</sub> and  $\alpha_1$ -adrenergic receptor antagonism.<sup>17</sup>

In conclusion, even though quetiapine may be indicated for the treatment of substance dependence, its potential for misuse should not be underestimated; therefore, it should be used with caution, especially in patients with a history of polysubstance abuse. Also, the possibility of misusing other atypical antipsychotics sharing common properties with quetiapine cannot be excluded.

*Drs. Paparrigopoulos, Karaiskos, and Liappas report no financial affiliation or other relationship relevant to the subject of this letter.*

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### Selective Serotonin Reuptake Inhibitor Add-On Therapy for the Negative Symptoms of Schizophrenia

**Sir:** I read with interest the recent meta-analysis by Sepehry et al.<sup>1</sup> of selective serotonin reuptake inhibitor (SSRI) add-on therapy for negative symptoms of schizophrenia and am concerned that their negative conclusion largely reflects methodological limitations.

The small number and heterogeneity of available studies make meta-analytic analyses at this time particularly vulnerable to confounds.<sup>2</sup> Further, optimal use was not made of available studies: all participants in our original study<sup>3</sup> received typical antipsychotics (the only ones available then), a fact easily clarified, and thus were eligible for subanalyses of that group. It was also plausible to include a controlled comparison of the effect of an SSRI and a non-SSRI antidepressant (rather than placebo) on negative symptoms.<sup>4</sup> Given the critical importance of differentiating primary and secondary negative symptoms, including studies not designed for negative symptoms introduces unacceptable confounds, an effect suggested by the positive results of the subanalysis when such studies are excluded.<sup>1</sup>

More generally, some issues require particular attention in studies of negative symptoms and augmentation. First, evidence

that negative symptoms differ in propensity and rapidity of response<sup>5,6</sup> requires use of assessment tools with adequate resolutions to detect different symptom response profiles. Second, while an antidepressant effect alone appears insufficient to ameliorate negative symptoms and a serotonergic mechanism is necessary to ameliorate them,<sup>4</sup> it is not known whether all SSRIs are effective. Inappropriate groupings of SSRIs can lead to confounds and may explain some discrepancies between reports. The effective doses of SSRI for anti-negative symptom effect are not known. There is evidence that they are lower than needed for antidepressant effect for fluvoxamine,<sup>7</sup> but data for other SSRIs are lacking. Third, the type of concomitant antipsychotic may be important, not only because of the presence/absence of serotonergic activity but also because the residual negative symptom profile at the start of augmentation may differ in patients treated with atypical and typical antipsychotics.

Undoubtedly, investigation of this complex area would benefit from better understanding of the mechanisms of SSRI-antipsychotic interaction. Of interest in this regard are our recent findings of unique changes in GABA-ergic, dopaminergic, and serotonergic systems in selected areas of the rat brain following coadministration of haloperidol and fluvoxamine.<sup>8,9</sup> These changes differed from those of the individual drugs and were not explained by pharmacokinetic interactions, and, importantly, some were similar to those following clozapine administration. Preliminary clinical studies showed changes in GABAergic, cytokine, and G-protein system markers in peripheral mononuclear cells of schizophrenia patients after addition of an SSRI to preexisting antipsychotic treatment.<sup>10</sup>

Hopefully, the new insights into the mechanisms of augmentation treatment and possible identification of biological markers will advance our investigations of negative symptoms and their treatment.

*Mr. Sepehry was shown this letter and declined to comment.*

*Dr. Silver reports no financial affiliation or other relationship relevant to the subject of this letter.*

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### Inconclusive Evidence for the Efficacy of Olanzapine in the Treatment of Negative Symptoms in Schizophrenia

**Sir:** In a recent systematic review of the pharmacologic treatment of primary negative symptoms in schizophrenia, my colleagues and I<sup>1</sup> concluded that there was a paucity of evidence regarding efficacy of treatments of primary negative symptoms and that the lack of standardized research designs had led to marked inconsistencies in results. A case in point was olanzapine's efficacy against primary negative symptoms. Of the 4 conducted trials, the only study to use selected patients with primary negative symptoms found no benefit<sup>2</sup>; 2 studies using path analysis suggested the reverse,<sup>3,4</sup> while a third was ambivalent.<sup>5</sup> Unfortunately, the positive finding in the recent (March 2007) small, Lilly-funded study of olanzapine in the treatment of primary negative symptoms of schizophrenia by Lindenmayer et al.<sup>6</sup> does not clarify the issue.

The main design fault is Lindenmayer and colleagues' use of a first-generation antipsychotic as a comparator. The mean dose of haloperidol used (17.11 mg) invariably induces secondary negative symptoms. The authors' argument that the concomitant use of benztrapine would negate any secondary negative symptoms is spurious. While coadministration may mitigate the effects of hypodopaminergia in the nigrostriatal and tuberoinfundibular tracts, it does not do so in the mesocortical tracts. Simply put, benztrapine does not protect a patient from the negative symptoms induced by haloperidol. Anticholinergics are not a treatment for negative symptoms; in fact, cholinesterase inhibitors are putative agents for the treatment of both negative symptoms and neurocognitive deficits in psychosis. Olanzapine, which does not induce secondary negative symptoms, would therefore perform better in a head-to-head comparison even if it had no beneficial effects on primary symptoms.

Theoretically, anticholinergics exacerbate negative symptoms (and neurocognitive problems) in psychosis, though, as with sedation secondary to histamine blockade, the effect is not dopaminergic and the symptoms are "pseudonegative" in origin. This potential for exacerbation would further worsen negative symptom (and neurocognitive) scores in the haloperidol group, though the difference between the two groups would be offset to a considerable degree by olanzapine's own penchant for "pseudonegativity" (and causing cognitive deficit) through its cholinergic and substantial histaminergic blockade.

A further problem in the study by Lindenmayer et al. was the prior use of first-generation antipsychotics. The washout period was not long enough to overcome iatrogenic negative and neurocognitive symptoms, which would continue to diminish during the study period in the olanzapine group. There should

have been within-group comparisons dependent on prior medication (first-generation or second-generation antipsychotic) to estimate the extent of this effect.

Lindenmayer and colleagues are to be commended on using patients with high levels of negative symptoms and low levels of secondary confounds (positive symptoms, depression, and extrapyramidal symptoms [which are a proxy marker for the emergence of negative symptoms in the absence of concomitant anticholinergics]), but they should have further factored out any possible effects using path analysis, especially given the trend toward abatement of all 3 of these secondary confounds in the olanzapine group. Other shortcomings include not reporting between-group differences in chronicity, which plays a crucial role in determining negative symptom response to antipsychotics (B.P.M.; P. D. McGorry, Ph.D.; A. S. Stuart, B.Appl.Sci. [Hons.]; manuscript submitted; 2007); not using a quality of life scale, rendering it unclear if any reduction in Positive and Negative Syndrome Scale ratings translates into improved life quality; and the racial demographics of the study population, which may prevent the generalizability of findings to females or white individuals.

*Dr. Murphy reports no financial affiliation or other relationship relevant to the subject of this letter.*

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#### Dr. Lindenmayer Replies

**Sir:** In his letter to the editor, Dr. Murphy opines against the use of a first-generation antipsychotic as a comparator in our study,<sup>1</sup> stating that "the mean dose of haloperidol used (17.11 mg) invariably induces secondary negative symptoms."

However, there is little evidence that haloperidol systematically induces secondary negative symptoms. In fact, 2 recent studies<sup>2,3</sup> comparing the effects of olanzapine, a second-generation antipsychotic with a very benign extrapyramidal symptom profile, with haloperidol at doses similar to those used in our study combined with benztrapine found no significant differences for positive or negative symptoms in schizophrenia between the 2 antipsychotics. Buchanan and colleagues<sup>2</sup> found no significant differences between olanzapine (20.3 mg/day)

and haloperidol (18.3 mg/day) combined with benztropine (4 mg/day) in outpatients with partially responsive schizophrenia. Also, Rosenheck and colleagues<sup>3</sup> found almost completely equivalent effects of haloperidol compared with olanzapine in most of their outcome measures. In addition, our concomitant and systematic use of benztropine in the haloperidol group may have further reduced the potential dose effect of haloperidol on negative symptoms. In support of this interpretation is the lack of difference in extrapyramidal symptoms in the 2 treatment groups, which was also shown in the Rosenheck et al. study.<sup>3</sup>

Dr. Murphy also states that the washout period used in our study from prior use of first-generation antipsychotics may not have been long enough to overcome iatrogenic negative and neurocognitive symptoms. We did conduct a within-group comparison of prior use of first- and second-generation antipsychotics (data not reported in the published study). Both the olanzapine and the haloperidol group had comparable exposure to both first- and second-generation antipsychotics (mean length of time on prior treatment with first-generation antipsychotics for the haloperidol group was 122.31 days [N = 8] and for the olanzapine group was 129.21 days [N = 5], and mean length of time on prior treatment with second-generation antipsychotics for the haloperidol group was 121.10 days [N = 14] and for the olanzapine group was 127.23 days [N = 11]). Furthermore, measures of chronicity were entirely comparable between the 2 groups: for example, the mean (SD) age at first psychiatric hospitalization for haloperidol was 18.19 (11.23) years and for olanzapine was 18.23 (11.76) years.

Further support that our dose of haloperidol may not have been associated with the aggravating iatrogenic effects Dr. Murphy suggests comes from a recent meta-analysis by Woodward et al.,<sup>4</sup> who examined the relationship between cognitive change and dose of haloperidol within the control arms of 17 prospective clinical trials comparing atypical and typical antipsychotics. Their results indicate that overall cognitive performance improved with haloperidol. Studies that used a low dose of haloperidol (< 10 mg) did not yield larger effect sizes for overall cognitive function measures or specific neuropsychological measures than studies that used a high dose (> 10 mg), although doses greater than 24 mg had deleterious effects. The mean haloperidol dose in our study was significantly below this threshold.

The authors also state that path analysis should have been used to further "factor out" any possible effects on negative symptoms of positive, depressive, and extrapyramidal symptoms. We feel that this statistical strategy has serious methodological shortcomings, which include uncertainties in the formulation of the model, recursiveness of the equations, and uncertainties in data interpretation. In addition, the causal path required in this type of analysis is specified by explicating deductive theory, and nothing in the statistical technique would indicate that the order of the paths is wrong. Finally, the sample size for this study was a total of 36 subjects. Adequate sample size is needed in path analysis to assess significance. Kline<sup>5</sup> recommends 10 times as many cases as parameters.

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*Dr. Lindenmayer has been a consultant to Janssen and Eli Lilly and has received grant/research support from Janssen, Eli Lilly, AstraZeneca, Bristol-Myers Squibb, Pfizer, and Organon.*

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#### Hypokalemia Following Rapid Titration of Quetiapine Treatment

**Sir:** Hypokalemia has been reported following regular treatment with typical antipsychotics in 13 Chinese patients<sup>1,2</sup> and 1 white individual<sup>3</sup> and following treatment with clozapine, the prototype of atypical antipsychotics, in 1 Chinese patient.<sup>1</sup> Overdose toxicity was demonstrated in a case report on remarkable hypokalemia after combined use of 2 atypical antipsychotics: an exceedingly large dose, 100 mg, of risperidone plus a therapeutic dose, 750 mg, of quetiapine.<sup>4</sup> Hypokalemia, though infrequently identified, can be a serious adverse effect of antipsychotics. For example, it may lead to QT interval prolongation and thereby life-threatening arrhythmias such as torsades de pointes.<sup>5</sup> However, whether regular treatment of atypical agents other than clozapine can induce hypokalemia remains unclear.

We here report a case of hypokalemia following standard-dose quetiapine monotherapy.

**Case report.** Mr. A, a 22-year-old Han Chinese man living in Taiwan, experienced aloofness, alogia, and social isolation for 3 months. His parents led him to visit a general physician clinic in 2006, where schizophrenia was suspected. He was given quetiapine 200 mg h.s. Two hours after the first dose of quetiapine, he developed drowsiness and was sent to our emergency department. Laboratory examination revealed electrocardiographic, urine/blood routine, and biochemistry measurements within normal limits, except for a plasma potassium level of 2.8 mmol/L and plasma sodium level of 137 mmol/L, indicating hypokalemia. The tentative diagnosis by an experienced psychiatrist was prodromal schizophrenia. Quetiapine treatment was discontinued, and supportive treatment with intravenous potassium supplementation was instituted in the intensive care unit. He was fully recovered; levels of electrolytes (including a plasma potassium level of 3.7 mmol/L), blood urea nitrogen, serum creatine, and serum aldosterone were within normal limits, and he was discharged 3 days later. Two weeks following his discharge, these laboratory data remained within normal limits, and he experienced no physical or neurologic sequelae.

Two months later, after a conflict with his father, Mr. A attempted suicide by taking 600 mg of the quetiapine prescribed earlier by the general physician. Conscious disturbances recurred. Plasma potassium concentration, checked at the emergency department, had decreased to 2.9 mmol/L and returned to 3.6 mmol/L after potassium supply. During the 2 episodes, the

patient was receiving no other medications. His score on the Naranjo adverse drug reaction probability scale<sup>6</sup> was 9.

Though the mechanism of drug-related hypokalemia is unclear, antipsychotics have been reported to inhibit the secretion of antidiuretic hormone (ADH) and/or the reabsorption of water and electrolytes in renal tubule, leading to an increase in the extrusion of potassium.<sup>2,3</sup> How antipsychotics might inhibit ADH secretion also requires elucidation. However, it has been suggested that D<sub>2</sub> agonists may increase ADH levels<sup>7</sup> and that ADH secretion may relate to dopamine activity.<sup>8</sup>

According to previous reports (as well as the current one), Han Chinese people may be more likely to experience hypokalemia with therapeutic dosages of typical or atypical antipsychotics than other ethnic populations. It has been indicated that Asian populations may differ from other races in response to antipsychotics<sup>9</sup> and require lower drug doses than white individuals<sup>10–12</sup>. Both pharmacokinetic factors<sup>13,14</sup> and pharmacodynamic factors<sup>9</sup> need to be considered. Since quetiapine is predominantly metabolized by cytochrome P450 (CYP) 3A<sup>15</sup> and Asian individuals have lower CYP3A activity than white individuals,<sup>16</sup> this between-race difference in pharmacokinetics may contribute to the current case.

In addition, as shown above, dopamine D<sub>2</sub> neurotransmission may modulate ADH secretion and thereby electrolyte imbalance,<sup>7,8</sup> and variances of the D<sub>2</sub> receptor gene (DRD2) may differ between populations.<sup>17</sup> For example, the Cys allele of the DRD2 Ser311Cys polymorphism is more common in Han Chinese than in the Western populations and is associated with better treatment response.<sup>17</sup> This pharmacodynamic factor may also play a role in the current case.

Other potential contributory factors in our case deserve attention, too. First, the initial dose, 200 mg, received by the current patient was much higher than the recommended dose of 25 mg b.i.d.—not to mention his suicide attempt using an overdose at 600 mg. Second, what the patient suffered was prodromal schizophrenia, and such individuals may be more vulnerable to antipsychotic side effects than patients with schizophrenia.<sup>18</sup>

This case suggests that quetiapine monotherapy, particularly at rapid titration, in Han Chinese, or in patients who have not yet achieved the definite diagnosis of schizophrenia, could cause hypokalemia. For such circumstances or populations, extra caution should be exerted and regular monitoring of electrocardiograms and plasma potassium levels is warranted.

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