

### QTc Prolongation: Chlorpromazine and High-Dosage Olanzapine

Dear Editor:

The electrocardiographic QT interval reflects ventricular depolarization (QRS complex) and repolarization (ST segment and T wave). It varies inversely with heart rate and is usually less than or equal to one-half the RR duration (1). The heart rate corrected interval (QTc) is normally less than or equal to 440 ms, and a QTc of over 500 ms characterizes an increased risk for developing dangerous cardiac dysrhythmias (for example, torsades de pointes) (2,3). This interval exhibits additional variability with sex, age, circadian variation, metabolic abnormalities, and exposure to selected pharmaceuticals. Antipsychotic agents are among the many medicines that can cause QTc prolongations: chlorpromazine, thioridazine, olanzapine, quetiapine, and ziprasidone can create this cardiac concern (3–7). Olanzapine is associated with such change in higher dosages but is generally better tolerated at conventional quantities (4,5). The following case report documents QTc prolongation in an elderly woman receiving chlorpromazine and quetiapine, which improved when she was taken off these drugs. Later, however, prolongation reoccurred while on high-dosage olanzapine, which was not evident on a lesser olanzapine dosage.

#### Case Report

A 66-year-old obese woman was hospitalized with diagnoses of schizoaffective disorder, hypertension, hypothyroidism, and hyperlipidemia. Chlorpromazine and quetiapine were among 13 medications that she had been prescribed. Initial laboratory reports evidenced normal serum chemistries, thyroid-stimulating hormone, and hemogram. Baseline electrocardiographic QTc prolongation at 450 ms was attributed to the antipsychotic medicines, which were discontinued.

Olanzapine 40 mg daily was prescribed, and 13 days later, the QTc was 416 ms.

The next day, olanzapine was increased to 60 mg, owing to severe agitation. Four days later, the QTc interval was 436 ms (20 ms lengthening). New serum chemistries, including calcium, magnesium, sodium, and potassium concentrations were normal; electrolyte imbalance or hypothyroid etiologies for QTc prolongation were unlikely.

Olanzapine 60 mg daily was deemed as the cause of this cardiac finding, and the dosage was reduced to 40 mg. Follow-up electrocardiograms the next morning and afternoon evidenced intervals at 393, 396, and 415 ms. After the olanzapine dosage was decreased, however, the QTc returned to a safer value.

Several antipsychotic medicines have been reported to be associated with QTc interval prolongation (3–7). Drug combinations, as in our case with chlorpromazine and quetiapine, may be an additional risk factor. The electrocardiogram helped to detect the cardiac conduction delay. It provided a clinical guide for discontinuing chlorpromazine and quetiapine and for prescribing olanzapine. It was not surprising to observe QTc prolongation with chlorpromazine and quetiapine that normalized once these drugs were discontinued. The QT interval with olanzapine was unremarkable until the dosage was 60 mg daily. The literature documents that olanzapine can cause QTc prolongation in various amounts; high-dosage olanzapine induces greater risk, but as little as 2.5 mg daily can also extend this interval (5,6). Our case demonstrates QTc prolongation that was still in the acceptable range with initiation of higher-than-conventional dosages of olanzapine. After the dosage was decreased, the QTc shortened to a safer value.

Thus, it is prudent to provide careful electrocardiographic monitoring in patients taking chlorpromazine and high-dosage olanzapine, in cases of antipsychotic drug polypharmacies, and in older people.

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### Should Lipids be Monitored During the First Year of Treatment with an Atypical Antipsychotic?

Dear Editor:

Recent studies have demonstrated a high prevalence of hyperglycemia and dyslipidemia in patients who are treated with atypical antipsychotics. The highest prevalence of these disorders has been observed with clozapine and olanzapine, but they have also been reported with risperidone and quetiapine (1–4). In a recent article, Meyer proposed quarterly fasting total triglycerides and cholesterol during the first year of atypical antipsychotic therapy, and many colleagues follow this recommendation (4). Recent pharmacoepidemiologic studies, however, suggest that a significant number of patients with schizophrenia discontinue their medication for various reasons within the first year of treatment. Glick and Berg reported the survival analysis of 2 clinical trials with olanzapine and risperidone in

schizophrenia (5). In the first study, 37% of patients treated with olanzapine discontinued their medication at 12 months follow-up, owing to adverse events or lack of efficacy. In the second study, survival analysis at 6 months demonstrated that 27% and 32% of all patients treated with olanzapine or risperidone, respectively, discontinued their medication. In a naturalistic study, Binder and others reported that only 36.2% (21/58) schizophrenia and schizoaffective disorder patients were still on risperidone at 2-year follow-up (6). Our own naturalistic study indicates that, among the individuals with schizophrenia or schizoaffective disorder treated with either olanzapine, risperidone, or clozapine at the time of their discharge from the hospital, 36%, 22%, and 8%, respectively, have discontinued their antipsychotic 1 year later (7). The reasons for discontinuing were failure to achieve a therapeutic effect, non-compliance, and adverse side effects. Thus, one has to question the cost-effectiveness of some of the proposed laboratory monitoring with atypical antipsychotics. Diabetic ketoacidosis can occur in the first few months after initiating clozapine and olanzapine, and the prevalence and short-term health consequences justify regular monitoring of glycemia during the first year of treatment. By comparison, the immediate health consequences owing to weight gain and dyslipidemia are not a major concern in the first year of treatment, and monitoring of lipid parameters cannot be justified economically. However, clinicians should make patients aware of the risk of dyslipidemia with atypical antipsychotics, and preventive measures such as diet and physical exercise should be encouraged early in the treatment.

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## Quetiapine May Induce Mania: A Case Report

Dear Editor:

Inducing manic or hypomanic symptoms is a well-documented risk during antidepressive treatment with different classes of antidepressants (1-3).

Recently, several case reports and a critical review have demonstrated a similar risk induced by atypical antipsychotics, such as olanzapine and risperidone (4). A serotonin (5-HT) receptor occupancy (5-HT<sub>2</sub> and 5-HT<sub>D2</sub>) hypothesis has been proposed to explain olanzapine and risperidone effects on mood (5), but other mechanisms are likely involved in the manic switch that is associated with these 2 atypical antipsychotics (4).

A case report of a woman affected by schizoaffective disorder with quetiapine-associated hypomania has been published. She developed a hypomanic episode after 5 weeks of quetiapine treatment (gradually titrated to 300 mg daily), which receded in 1 week after quetiapine discontinuation (6).

We report a further case of possible induction of manic episode associated with quetiapine treatment in a patient with a schizophreniform disorder.

### Case Report

A 23-year-old woman with a DSM-IV diagnosis of schizophreniform disorder was hospitalized for a recent onset of psychotic symptoms, including anxiety, perplexity, and persecutory and somatic delusions. The patient had no history of substance abuse or manic or hypomanic episodes.

From the first day of hospitalization, a treatment with haloperidol 10 mg daily, venlafaxine 75 mg daily, and diazepam 2 mg daily was started, but without improvement. Next, venlafaxine and haloperidol were discontinued, and a trial with quetiapine was started and titrated to 400 mg daily over 3 weeks. Gradually, her psychotic symptoms improved, but during the 4th week of treatment, insomnia, hyperactivity, irritability and hostility, elated mood, and grandiosity emerged.

Because of the suggestive temporal relation between the introduction of quetiapine and the onset of manic symptoms in a patient with no history of substance abuse or manic episodes, mania secondary to quetiapine was hypothesized. Quetiapine was discontinued and zuclopentixol and lorazepam were started. Manic symptoms gradually disappeared in the 10 days that followed and did not reappear during the 3-week hospitalization period.

We have described a possible case of mania induced by quetiapine in a patient with schizophreniform disorder. The gradual onset of manic symptoms during quetiapine treatment and the rapid remission with discontinuation of the drug in a patient without a history of mania and without past or current substance abuse seems to support the possibility that quetiapine was responsible for inducing the manic episode. In our case, which is similar to Benazzi's case, manic symptoms appeared slowly at a moderate quetiapine dosage (6). This seems to support the hypothesis proposed for risperidone, with which quetiapine shares biochemical features; specifically, at high dosages, dopaminergic blockade action shows antimanic properties, while, conversely, at smaller dosages, the mania-inducing effects could result from the 5-HT<sub>2</sub> antagonistic action, as well as the ensuing dopamine disinhibiting effects (5).

Although further observations are necessary, clinicians should be aware that quetiapine (as olanzapine and risperidone) may play a role in inducing mania.

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### Insight, Knowledge, and Beliefs About Illness in First-Episode Psychosis

*Dear Editor:*

Psychoeducation about psychosis is a valuable therapeutic strategy in that it may improve understanding of the illness itself and potentially modify patients' behaviours and attitudes (1). In our comprehensive Early Psychosis Program (EPP), we offer education about the illness in family intervention sessions and through case and psychiatric management with a specifically designed Psychosis Education Group (2). We describe here a study that explored the impact of providing education about psychosis to individuals experiencing a first episode of a psychotic illness. Of the 78 subjects, 57 were men and 21 were women (mean age 24.7 years). They had been attending EPP as outpatients for between 12 and 30 months and had either full or partial remission of positive symptoms. We designed a multiple-choice questionnaire (the Knowledge About Psychosis Questionnaire) based on existing knowledge questionnaires in the literature and on the material taught in our program (3). We

used the Insight Scale (4) to obtain information on insight regarding psychiatric illness (that is, attribution of symptoms, awareness of illness, and need for treatment). We administered the Personal Beliefs About Illness Questionnaire (PBIQ) (5) to obtain patients' current beliefs about their illness and the degree to which patients felt that the social and scientific beliefs about their illness reflect statements about themselves. The PBIQ assesses beliefs about control over the psychotic illness; about the perception of the self as illness; and about expectations, stigma, and social containment. Both scales have good test–retest reliability and validity (4,5).

Overall, individual patients were knowledgeable about their illness: 90% answered correctly on at least 75% of the items. Good knowledge was significantly associated with good insight about the psychotic illness ( $P < 0.05$ ). However, having good knowledge about the facts of the illness was not related to individuals' beliefs about the illness. Further, those who demonstrated good insight did not necessarily demonstrate positive beliefs about the illness. Pearson correlational analyses revealed that those demonstrating good insight endorsed items on the PBIQ that suggested lack of control over the illness ( $P < 0.001$ ), expectations of requiring care for the illness ( $P < 0.01$ ), experiences of stigma ( $P < 0.05$ ), and the need for social containment ( $P < 0.05$ ).

These data imply that offering education to individuals with psychosis, even when they demonstrate good insight into the illness, may not be enough. Rather, these data support the need to understand and address the beliefs individuals hold about their psychosis—beliefs that tend to reflect negative statements about themselves. Such beliefs may lead to secondary morbidity following illness onset. Recent support for cognitive-behavioural therapy (CBT) with first-episode subjects (6) implies that CBT may be an appropriate intervention

to help challenge some of the personal beliefs that may impact negatively on outcome.

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### The Symptoms of Atypical Depression

*Dear Editor:*

Studies of the diagnostic criteria of atypical depression have recently increased. In one such study, Parker and others sampled individuals with major depressive disorder (MDD) (1) and, after finding weak correlations and associations among only some atypical symptoms, reported weak support for DSM-IV-TR atypical features criteria (2). (According to these criteria, an individual must present a bipolar or MDD major depressive episode or dysthymic disorder, always including mood reactivity plus at least 2 of the following: increased weight or appetite, hypersomnia, significant energy loss, and long-standing sensitivity to interpersonal rejection, but no melancholic or catatonic features.) In another study, Posternak and Zimmerman found no correlations among atypical symptoms in subjects who mainly suffered from MDD (3). An

important limitation of these studies is that conclusions are based only on subjects with MDD, while in the DSM-IV-TR, atypical features can occur in individuals with either depressive or bipolar disorders (BDs). Atypical depression may be different in BD, compared with MDD. Studies by Benazzi (4) and Angst and others (5) found atypical features to be much more common in BD II than in MDD, which accords with the official DSM-IV-TR statement (p 421). In the Benazzi study of consecutively presenting outpatients, atypical features were present in 53.5% of subjects with BD II ( $n = 241$ ) and in 23.7% of subjects with MDD ( $n = 164$ ) ( $z = 5.9, P = 0.0000$ ) (4). These 2 studies have an important difference from the Parker and others (1) and Posternak and Zimmerman (3) studies: they include mixed samples (that is, BD II plus MDD). Benazzi found significant associations among atypical symptoms (4). However, while most atypical symptoms were significantly associated in Benazzi's BD II sample, only a few were significantly associated in his MDD sample. This suggests that atypical depression may differ in depressive and bipolar disorders (6). Angst and others also found significant associations among atypical symptoms (5), but in the Angst and others study, atypical depression was not studied separately in the BD II and MDD sample (which were combined in the analyses). Parker and others (1), Posternak and Zimmerman (3), and Angst and others (5) concluded that mood reactivity should not have the priority it has in DSM-IV-TR (according to which it must always be present). Benazzi (4) came to the same conclusion, but only for the MDD sample. In the BD II sample, mood reactivity was significantly associated with atypical symptoms, and depression patients with mood reactivity had significantly more atypical symptoms than did depression patients without mood reactivity. These findings support the inclusion of mood reactivity among the atypical features in BD II but not in MDD. Consequently, atypical depression should probably be studied independently in MDD and in BDs. Parker and others stated that hypothesizing a different response to antidepressants to support the diagnostic validity of atypical features

(currently its main validator) is an unusual approach (1). Family history is a more important diagnostic validator (6,7). It has been shown that atypical features are strongly associated with a positive family history of BD (8)—a finding further supporting the distinction between atypical depression in MDD and in BD. Further studies are required to find a new definition of atypical depression, beyond that offered in the DSM-IV-TR.

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## Potential Risk of Diabetes Mellitus With the Use of Atypical Antipsychotic Medication

Dear Editor:

For the past 10 years, several atypical antipsychotics have been used to alleviate the symptoms of psychosis in a diverse patient population suffering from schizophrenia. During this time, clinicians have encountered benefits as well as a host of side effects in this patient population. Weight gain and the development or exacerbation of diabetes mellitus (DM) continue to be serious issues that have

forced clinicians to vigilantly follow up their patients' metabolic profile to prevent serious consequences.

The following case illustrates the need to monitor individual patients, not only for improvement of psychosis but also for DM as an adverse side effect.

## Case Report

Mr B, aged 62 years, is an African American who has suffered from schizophrenia for more than 45 years and was hospitalized owing to exacerbated symptoms of psychosis. He had no history of comorbid substance abuse. He had been free of diabetes, and his family history is negative for DM. His body weight was in the normal range for his age and height, and there had been no dietary changes. Hemoglobin A1c was within normal range. He was started on olanzapine, and the dosage titrated to 20 mg within a few days. His psychotic symptoms began to decrease in intensity, although they had not fully resolved after about 14 days. At this time, his blood glucose rose to almost 200 mg and remained high, requiring an oral hypoglycemic agent. Because of his severe psychotic illness, he was started on ziprasidone, a novel antipsychotic used to treat psychosis, in the hope of gradually weaning him off olanzapine. His blood glucose levels are now back to normal. With the combination of ziprasidone titrated to the optimal dosage of 80 mg twice daily and olanzapine 20 mg at bedtime, his psychosis is well controlled, and he can be discharged in the near future. However, the emergence of DM remains a serious issue in this patient. The rest of his laboratory tests remain normal at this stage.

## Discussion

The mechanism for antipsychotic-induced DM is not clear in this case. There was no weight gain during his short period of hospitalization. We hope that over time the antipsychotic crossover will continue to effectively treat his psychosis and that his blood glucose will revert to its pretreatment level, so that the oral

hypoglycemic agent can be safely discontinued.

Several retrospective data analyses of patients with diabetes taking antipsychotics have yielded an increased risk of either development or exacerbation of this metabolic condition—up to 3 times the risk with olanzapine, 7 times the risk with clozapine, and 2 times the risk with conventional high-potency antipsychotics (1).

Therefore, careful and regular monitoring for diabetes pre- and posttreatment continues to remain a significant part of the psychopharmacotherapy of schizophrenia. The availability of newer antipsychotics such as ziprasidone and aripiprazole may be a step forward in managing this situation.

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### Clozapine-Induced Aplastic Anemia in a Patient With Parkinson's Disease

Dear Editor:

Psychosis is a common complication of the drug treatment of Parkinson's disease (occurring in approximately 25% of patients) and therefore constitutes a serious public health problem. All patients suffering from idiopathic Parkinson's disease, and especially elderly patients with dementia, are at risk of developing delusions or hallucinations. The most prominent psychotogenic factors are dopaminomimetic agents, which may induce dopamine hypersensitivity in the frontal and limbic dopamine projection regions and consequently, either directly or indirectly, elicit psychotic signs and symptoms (1). A Parkinson's disease-related cholinergic deficit

combined with an age-related further loss of cholinergic integrity also plays a prominent role (1). Treating this complication is difficult: because of their selective dopamine receptor antagonistic effects, most typical antipsychotic drugs worsen motor symptoms of Parkinson's disease. As a consequence of a nonselective antagonism at both serotonergic and dopaminergic receptors, atypical antipsychotics such as clozapine or olanzapine are associated with fewer extrapyramidal side effects (2). Clozapine was the first atypical antipsychotic drug to be introduced into clinical use in several European countries, in the late 1960s (3). Clozapine treatment is associated with wide side effects that include the following: blood-cell dyscrasias, benign granulocytopenia, transient granulocytosis, and a risk of agranulocytosis as high as 0.5% to 1% (4); transient fever in up to 50% of the patients; sedation; and considerable body-weight gain. The mechanisms underlying these side effects are still unknown, but recent data suggest that the metabolism of clozapine and its immunomodulatory effects may play a role. Aplastic anemia in all its features emerging during clozapine therapy has not been documented in the literature. We present a case of clozapine-induced aplastic anemia.

### Case Report

A 53-year-old man with Parkinson's disease (according to ICD-10 criteria) developed a dopamine-induced psychosis with hallucinations. Because of his persisting psychotic symptoms, he was admitted to a psychiatric hospital, and antipsychotic pharmacotherapy of 50 mg clozapine daily was started. He developed fever after 1 week, and his blood tests revealed abnormalities (neutrophil count < 500/L, platelet count 93 000/L, and reticulocyte count < 20 000/L). Clozapine therapy was discontinued and he was admitted to our clinic. According to the criteria of the International Aplastic Anemia Study Group, we diagnosed a severe form of drug-induced aplastic anemia (neutrophil count < 500/L, platelet count 89 000/L, and reticulocyte count < 20 000/L). He received blood transfusions, and we started therapy with hematopoietic growth factors (r-metHuG-CSF) (5) and

antibiotics. The Parkinson's disease was treated with dopamine and apomorphine. After 14 days, he was responding to the therapy, and the aplastic anemia disappeared. The psychosis with delusions and hallucinations was still evident, and we established a neuroleptic therapy with quetiapine. The therapy with hematopoietic growth factors was discontinued.

We hypothesize that clozapine induced the severe aplastic anemia. The major classes of myelotoxic drugs are known, but the mechanisms by which certain agents cause aplastic anemia are still unclear. We suggest cautious use of clozapine in patients with Parkinson's disease.

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### Early-Onset Obsessive–Compulsive Disorder

Dear Editor:

Studies have reported high prevalence rates (6-month prevalence of 0.5% to 1%) of obsessive–compulsive disorder (OCD) in children and adolescents (1). Although the childhood onset-age of OCD in most clinical samples has ranged from age 6 to 11 years (2), the disorder has been found in children as young as age 3 years. We report the case of patient

with early-onset OCD who presented for psychiatric consultation many years after the onset of illness.

### Case Report

Mr A, age 16 years, is a slow-to-warm-up high-school student from a middle socioeconomic background. He presented for the first time to the clinic with a 2½-year history of school refusal and irritability. On clarification, it was apparent that from a very young age (even before age 5 years) he was excessively concerned about dirt. He would avoid looking at the toilet, even while using it, take an abnormally long time washing his face (his clothes getting wet in the process) and bathing, and would not allow anyone to use his towels. He would also avoid using toilets outside his own house whenever he went on a trip. About 2½ years before presenting to the clinic, he also began to have obsessive images of a dirty bathroom and toilet. Further, he began to fear that he would forget lessons studied and, hence, fail to answer either in class or during examinations. Consequently, he avoided exams and refused to go to school. He also thought that people were talking about him on the road and had checking compulsions yielding to these obsessive doubts, fears that books given to friends might get lost, compulsive reassurance seeking, repeated intrusive ruminations about events during the day, and thoughts that he would be responsible for something bad happening. He was also found to have a history suggesting separation anxiety disorder of childhood, sibling rivalry, and oppositional tendencies, for which psychiatric consultation had not been sought. The family history suggested unspecified mental illness in his maternal grand-aunt and maternal uncle, possible depressive illness in his paternal great-grandmother, and subclinical obsessive-compulsive symptoms in his mother's maternal uncle. Although he had poor insight and was uncooperative for treatment at the time of presentation,

he started showing response to sertraline (up to 150 mg daily). Later, he started cooperating with exposure- and response-prevention therapy for his contamination obsessions and with audioexposure therapy for his obsessive fear of forgetting lessons learned. At the end of 4 weeks' inpatient treatment, his obsessions and compulsions showed significant improvement.

This case highlights the fact that OCD may have onset at a very early age and is in keeping with the earlier findings of early onset being associated with male sex and positive family history (3). The long time-lag before this case actually presented to a psychiatrist indicates the need for increased awareness among professionals, especially because the illness arises at a developmentally important period.

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### Treatment Noncompliance With Orally Disintegrating Olanzapine Tablets

*Dear Editor:*

Recently, Chue and colleagues suggested that new formulations of antipsychotics that are fast-dissolving in the mouth, such as orally disintegrating olanzapine tablets, are welcome. They are seemingly impossible to "cheek" and may improve

medication adherence (1). In selected patients, this is true. However, such novel drug formulations are no panacea against noncompliance, which was exemplified by a patient who managed to be noncompliant with fast-dissolving olanzapine tablets (2).

### Case Report

Ms A was a 52-year-old woman with chronic schizophrenia and tardive dyskinesia and a long history of noncompliance with antipsychotics, resulting in a cyclical pattern of hospitalizations that alternated with homelessness. Untreated, she was hostile, disorganized, and dishevelled. With antipsychotic treatment, she was pleasant, was able to follow ward routines, and took pride in her appearance, with great concern for potential weight gain. She never regarded herself as ill and always denied the need for medication.

After being involuntarily hospitalized, a 6-month clozapine trial failed, because the patient remained adversarial to taking medications. Despite great staff effort, she decompensated twice in hospital, owing to noncompliance (corroborated by plasma levels).

After she agreed to try out this newly formulated medicine, an olanzapine wafer trial was initiated. Although she was apparently compliant, no clinical improvement occurred after several weeks of olanzapine wafers at a dosage of 20 mg daily. A steady-state olanzapine plasma level was unexpectedly low (8.5 ng/mL). Finally, a nurse observed the following "cheeking" technique: the patient put the Zydys wafer up behind her front teeth near the gum line. It appeared that she kept her mouth dry to allow the wafer to stick in place. In this way, she managed to produce the wafer largely intact, minutes after it was administered. After this experience, she was started on haloperidol decanoate.

## Discussion

Patients who appear treatment-resistant could be noncompliant with antipsychotics. This patient had several risk factors for noncompliance: lack of insight into her illness or of medication benefit, a long history of noncompliance, and severe side effects to antipsychotics (3). We nevertheless did not consider noncompliance as a likely possibility, owing to the supervised medication dispensation and a prima facie "foolproof"

medication administration method. In hindsight, this was a mistake. Still, patients must be observed closely to ensure that the wafer disintegrates completely and is swallowed, because buccal absorption is negligible.

Thus, this case serves as a reminder that fast-dissolving oral medication is no substitute for parenteral medication.

## References

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