

## Intranasal Ketamine for Intermittent Explosive Disorder: A Case Report

**Sir:** Ketamine is an *N*-methyl-D-aspartate blocker. Nasal administration has been used successfully to abort one type of paroxysmal neurologic disorder, namely migraine.<sup>1,2</sup> This case describes successful use to abort rage episodes refractory to multiple medical and behavioral interventions.

**Case report.** Mr. A, a 20-year-old man, has a lifelong history of rages following denial of perseverative requests. There was often postictal regret of severe intensity, e.g., holding a knife to himself. Although the frequency of these episodes remained constant with age, perhaps 2 to 3 times daily, as the patient's physical strength increased with age he could no longer be contained by parental physical restraint. At age 18, parental injury was common and the police were called to the house as often as twice a week.

Medical history is suggestive for metabolic encephalopathy given prenatal stroke, focal epilepsy, one block exercise tolerance with hyperthermia, and unexplained hospitalization at 14 years of age with elevated creatine phosphokinase levels. Family history is germane as Mr. A's father has a history of severe medically refractory migraine and his sister has a history of episodes of confusion. Diagnostic review reveals magnetic resonance imaging evidence for prenatal stroke in the left middle cerebral artery distribution, negative surface video electroencephalogram monitoring during 2 rages, positron emission tomography evidence for corresponding left frontal-parietal hypoperfusion with possible medial temporal lobe involvement, and multiple negative serologic tests for classical metabolic disorder.

Failed medical interventions for anger include 7 anticonvulsants titrated to toxicity (phenobarbital, divalproex, topiramate, gabapentin, lamotrigine, clonazepam, and topiramate), 6 antidepressants (paroxetine, sertraline, clomipramine, imipramine, fluvoxamine, and bupirone), 4 antipsychotics (haloperidol, olanzapine, quetiapine, and risperidone), and clonidine, propranolol, lithium, and tamoxifen. Vagal nerve stimulator implantation was declined by 1 neurologist citing an absence of current epilepsy.

After an emergency room visit at 18 years of age resulted in involuntary treatment referral, Mr. A's family provided consent to use ketamine. Ketamine was considered given the density of his father's migraine. Reasoning from analogy with observed variable phenotypic expression in the channelopathies, it seemed reasonable to try an agent shown to be effective in migraine to abort a distinctly different neuropsychiatric event. In the following 16 months, as-needed doses of intranasal ketamine up to 60 mg over 4 hours generally kept rages under control. Tolerability was excellent, with initial prompting by parents replaced by requests for use with time. Cumulative doses greater than 200 mg daily, however, produced hallucinosis.

Ketamine is the most widely used anesthetic in the world. Previous reports only describe intramuscular or oral use to acutely manage agitated or explosive patients.<sup>3-6</sup> The intranasal route, as shown in this report, offers additional advantage in terms of speed of action and ease of use by the general public.

Use of ketamine remains relatively unexplored in rage episodes or other paroxysmal events such as panic, catatonia, or

surface null electroencephalogram eye closure seizures. Risks of hallucinosis, addiction, or posterior cingulate damage need to be considered with each individual case.

*Dr. Berner reports no financial or other relationships relevant to the subject of this letter.*

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## Cognitive Facilitation and Behavioral Disinhibition With Benzodiazepine: A Case Report

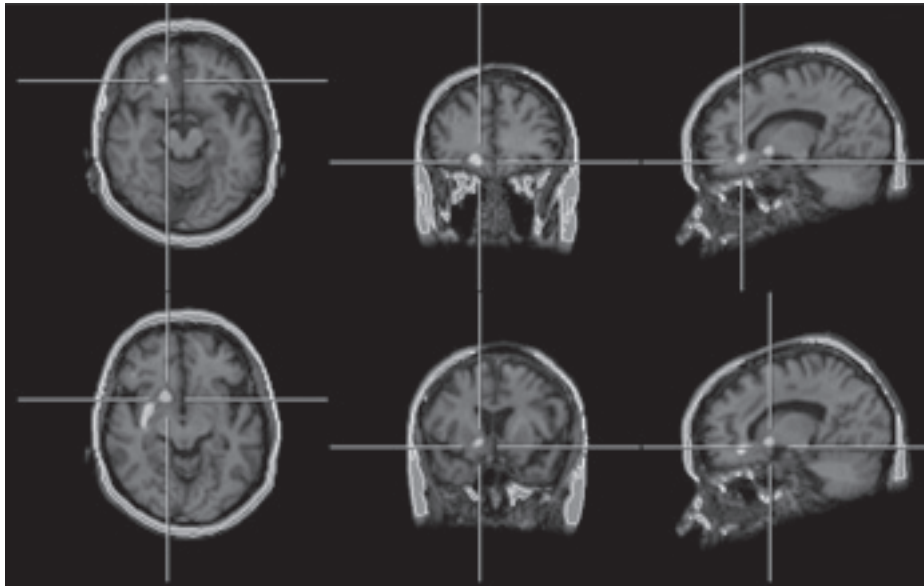
**Sir:** Although paradoxical effects of  $\gamma$ -aminobutyric acid (GABA)-ergic medications (excitation instead of sedation) are well-known, they have received no satisfactory explanation. We report the case of a 54-year-old woman with schizophrenia, in which we were able to observe this clinical pattern and its neural correlates.

**Case report.** The patient was in her forties, working as an assistant professor at a university, when she developed mostly negative symptoms. She did not engage in any new professional endeavors and became careless and apathetic. Following benzodiazepine intake, she enjoyed an increase of her wakefulness, and recovered some abilities to have a conversation and to make plans. Her benzodiazepine intake became uncontrolled, and 8 years ago, after taking bromazepam, she killed her husband with a chopper.

She had spent 2 years in prison when she came to our psychiatry department in November of 2001 with a probation order. The neuropsychological assessment showed a minor dysexecutive syndrome, and the single-photon emission computed tomography (SPECT) showed frontotemporal hypoperfusion. Both neuropsychological status and SPECT hypoperfusion were stable over the next 4 years, a pattern that ruled out frontotemporal dementia. Therefore, she received the diagnosis of late-onset schizophrenia (DSM-IV criteria). Various antidepressant treatments, including electroconvulsive therapy, and antipsychotic medications, including clozapine, provided no major improvement.

On 2 occasions, she was hospitalized for acute excitation without confusion, and benzodiazepine metabolites were

Figure 1. Axial, Coronal, and Sagittal SPECT Showing Increased Blood Flow With Zolpidem in Orbitofrontal Cortex (top line) and Striatum (bottom line)



Abbreviation: SPECT = single-photon emission computed tomography.

detected in urine samples. In order to better understand this benzodiazepine side effect, we decided to begin treatment with zolpidem, a selective agonist of  $\alpha_1$  subunit containing GABA type A receptors with no anxiolytic properties.<sup>1</sup> Twenty minutes after ingestion of 20 mg of zolpidem, the patient reported a strong feeling of well-being without any sedation. She also showed a considerable increase of her verbal fluency, and she started to plan some travels and hobbies such as diving. Six hours after intake, she returned to her usual condition. Relative to a baseline SPECT, SPECT with injection 30 minutes after zolpidem ingestion showed a cerebral blood flow increase of 15% to 25% in the right orbitofrontal cortex, inferior frontal gyrus, striatum, supplementary motor area; in the left premotor cortex; and in the bilateral posterior cingulate (see Figure 1).

Apart from its hypnotic properties, zolpidem has been shown to markedly improve catatonia.<sup>2</sup> It may modulate orbitofrontal-striatal loops that are GABAergic and are thought to be deficient in patients with catatonia.<sup>3</sup> Improvement of a Broca's aphasia has also been demonstrated with zolpidem, in a patient with a subcortical lesion including the striatum, with an increased perfusion in Broca's area, in mesial frontal and orbitofrontal cortex.<sup>4</sup>

Taken together with the pattern observed in our patient, these data suggest a key role for the orbitofrontal cortex in paradoxical effects, i.e., cognitive facilitation or excitation instead of sedation. Orbitofrontal modulation may also subserve the feeling of well-being reported by the patient.<sup>5</sup> We suggest that patients with functional deficiency or lesions in orbitofrontal-striatal loops, which are supposed to mediate socially critical restraint, may present paradoxical effects of benzodiazepines. Clinicians should be aware both of the potential benefit and of the medico-legal risks of the GABAergic medications in such cases.

*The authors report no financial affiliations or other relationships relevant to the subject of this letter.*

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## Applicability of the Oral Glucose Tolerance Test in Assessing Prevalence and Incidence of Diabetes Mellitus in Schizophrenia

**Sir:** In their very interesting article “Screening for Diabetes and Other Metabolic Abnormalities in Patients With Schizophrenia and Schizoaffective Disorder: Evaluation of Incidence and Screening Methods,”<sup>1</sup> van Winkel et al. report on use of an oral glucose tolerance test (OGTT) in 415 mainly inpatients (73.7%) in a Belgian psychiatric hospital. The numbers involved convincingly show that OGTT is a feasible option in the diagnosis of (pre)diabetes in schizophrenia.

The study, nevertheless, raises some methodological questions.

**Point 1:** The character of the study. The study is described in the Introduction as a report on “baseline data of . . . prospectively monitored schizophrenic patients.”<sup>1(p1494)</sup> This description suggests a prospective study: the terms *baseline* and *prospective* are terms normally indicative of an intervention and measurement of its effects. However, no systematic interventions are described, and no follow-up measurements have been reported. Moreover, the study is characterized in the Discussion as “a cross-sectional study.”<sup>1(p1498)</sup> So, what is it, a prospective or a cross-sectional study? My suggestion is to drop the terms *baseline* and *prospective* and to consider this study cross-sectional. If I am right, this suggestion opens up the possibility of comparison with other cross-sectional studies using the OGTT as a diagnostic instrument (see point 4).

**Point 2:** The status of the results. The authors maintain that the results of the screening are incidence rates. One of the arguments put forward is that previous routine fasting plasma glucose levels—before entering the study—had not revealed diabetic glucose abnormalities. I think that one of the main points of the article is that the authors have convincingly shown that routine measurement of fasting plasma glucose is in itself insufficient to detect disturbances in glucose metabolism and that more sensitive measurement, OGTT, is necessary. If we take this argument seriously, and I see no reason not to, then we should refrain from comparing the results of an insufficiently sensitive screening with those of the sensitive screening: because the OGTT is more sensitive, we should consider all patients who have been screened otherwise as unscreened. The rates found are those of a cross-sectional study, which means they are prevalence—and not incidence—rates.

**Point 3:** Prevalence of diabetes mellitus in comparison with other small pathophysiologic studies using OGTT<sup>2-4</sup> (Table 1).

- a. Newcomer et al.<sup>5</sup> studied 48 patients using a modified OGTT. According to the World Health Organization diagnostic criteria,<sup>6</sup> the glucose level at 120 minutes after 75-g glucose load determines whether diabetes is present (glucose timepoint = 120  $\geq$  11.1 mmol/L) or not (glucose timepoint = 120  $\leq$  11.0 mmol/L). The modified OGTT Newcomer et al. used,<sup>5</sup> a lower glucose load of 50 g and a shortened afterload time of 75 minutes, severely complicates any comparison with those results from a standard OGTT.
- b. Using standard OGTT, Cohen et al.<sup>7</sup> studied a mainly (64%) outpatient Dutch population with schizophrenia or schizoaffective disorder. The prevalence of previously undiagnosed diabetes mellitus was 6.5%, a rate that has been confirmed by the present Belgian study.<sup>1</sup> The almost identical prevalence figures are a surprise, consid-

ering the fact that the Dutch population clearly was more at risk, with a higher mean age (40.8 years vs. 34.7 years) and a higher mean weight (body mass index: 28.1 vs. 25.8) than the Belgian population.

**Point 4:** Incidence rates in comparison with the other studies (Table 1). The authors do present real incidence figures about a substantial subcohort of their population. After 1-year follow-up, 4.17% (10 of 240 patients) had contracted diabetes mellitus, comparable with “other incidence rates in patients treated with antipsychotics that ranged from 4.7% to 7.3%.”<sup>1(p1497)</sup> The 3 quoted studies deserve a closer look.

- a. The incidence rate of 7.3% clearly stems from the study by Leslie and Rosenheck,<sup>8</sup> who summarize their results as follows: “7.3% of the patients received a diagnosis of diabetes mellitus during the follow-up period, representing an annual incidence rate of 4.4%.”<sup>1(p1709)</sup> The 1-year incidence rate should therefore be corrected: not 7.3%, but 4.4%.
- b. The second quoted study (Miller et al.<sup>9</sup>) found an annual incidence of diabetes mellitus of 4.7%, but in a mainly nonschizophrenic population. Only 13% of the patients were diagnosed with schizophrenia; the majority was diagnosed with psychiatric disorders such as major depression (47%), dysthymia (36%), bipolar disorder (28%), and anxiety disorder (25%). The third study (Lambert et al.<sup>10</sup>), with an annual diabetes mellitus incidence rate of 6.9%, was (also) conducted in a “population of individuals with a variety of psychiatric diagnoses.”<sup>1(p922)</sup> The relevance of this incidence rate, originating from such a diverse psychiatric population, for patients with schizophrenia is a very interesting and relevant topic for a methodological debate but is as yet unsuitable to be represented as an established scientific fact.

All in all, only 1 study conducted in patients with schizophrenia (Leslie and Rosenheck<sup>8</sup>) with a very similar outcome (4.4%) remains for a comparison with the 4.2% rate found by van Winkel et al.<sup>1</sup>

In conclusion, 2 large-scale European (Belgian<sup>1</sup> and Dutch<sup>7</sup>) studies, in both inpatient and outpatient populations with schizophrenia or schizoaffective disorder, have shown that OGTT is a feasible option for the diagnosis of diabetes mellitus in this metabolically vulnerable group of patients. The diabetes mellitus prevalence rates were strikingly similar, despite relevant differences in the 2 major diabetes mellitus risk factors age and weight, confirming earlier doubts on the relevance of these risk factors for diabetes mellitus in schizophrenia.<sup>11,12</sup>

The rates of the 1-year diabetes mellitus incidence in schizophrenia, 4.2% and 4.4%, are based on the only 2 studies published so far (van Winkel et al.,<sup>1</sup> Leslie and Rosenheck<sup>8</sup>). Further research into the risk factors for this disturbingly high rate of diabetes mellitus is clearly needed.

*Dr. Cohen has received honoraria from Janssen Cilag and AstraZeneca and has served on the speakers or advisory boards of Eli Lilly and Bristol-Myers Squibb.*

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Table 1. Diabetes Mellitus (DM) Prevalence and Incidence in Schizophrenia

Variable	Database Studies			OGTT Studies	
	Lambert et al (2006) <sup>10</sup>	Leslie and Rosenheck (2004) <sup>8</sup>	Miller et al (2005) <sup>9</sup>	van Winkel et al (2006) <sup>1</sup>	Cohen et al (2006) <sup>7</sup>
Population characteristic					
Psychiatric diagnosis	Various S: 65%–85% <sup>a</sup>	S	Various S: 13%; OP: 12%	S, SA	S, SA
Population size, N	332	56,849	7381	415	200
Age, y	55.4	NA	40.4	34.7	40.8
Male, %	87	NA	43	67	70
Body mass index, kg/m <sup>2</sup>	29.1	NA	NA	25.8	28.2
Inpatient care, %	NA	NA	NA	74	14
Sheltered living, %	NA	NA	NA	0	22
Outpatient care, %	NA	NA	NA	26	64
Results					
DM prevalence, %	NA	NA	NA	6.3 <sup>b</sup>	6.5 <sup>b</sup>
1-year DM incidence, %	6.9	4.4	4.7	4.2 <sup>c</sup>	NA

<sup>a</sup>Percentage of nonschizophrenic patients varies according to prescribed atypical antipsychotic.

<sup>b</sup>Pre-existing DM excluded.

<sup>c</sup>N = 240.

Abbreviations: NA = not applicable, OGTT = oral glucose tolerance test, OP = other psychosis, S = schizophrenia, SA = schizoaffective disorder.

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### Drs. van Winkel and De Hert Reply

**Sir:** We appreciate the comments of Dr. Cohen on our study. Our study in the first place is a clinical monitoring routine, of which the results are systematically being collected and analyzed. More specifically, the vast majority of patients treated

with antipsychotic medication in our hospital and affiliated services are being screened and monitored for metabolic abnormalities. This screening routine was started in November 2003, and inclusions have been ongoing since then. At their first assessment (“baseline assessment”), patients are screened with an oral glucose tolerance test (OGTT), an electrocardiogram, and routine clinical and laboratory assessments. After the baseline screening, the patients usually have an OGTT every 3 months. The study population thus is a naturalistic, dynamic cohort that is being followed up prospectively. Our study reports on the baseline assessments of all patients screened in the first 2 years after starting the protocol (N = 415). As our study reports only on the baseline assessments, we agree with Dr. Cohen that it mostly resembles a cross-sectional study, as also stated in the Discussion of our article.

Nevertheless, the rate of new diagnoses that are being recorded in a population over a certain duration of time can be used to estimate incidence rates. Similar approaches have been used in the literature, for example, to estimate the incidence of diabetes type II in the Belgian general population.<sup>1</sup> In essence, the study by Leslie and Rosenheck,<sup>2</sup> which we have cited in our article and to which Dr. Cohen refers, uses a comparable approach, as they estimate incidence by the number of new diagnoses in the database of the U.S. Department of Veterans Affairs. We do agree with Dr. Cohen that this approach has some methodological limitations and thus that the reported rate of 3.2% is an estimate of the actual incidence risk rather than an actual assessment. Because of these methodological limitations and the observation that 3.2% is a very high incidence estimate, we have elaborated further on this incidence rate in our article, evaluating the credibility of such a high estimated incidence rate. We argue that it is unlikely that this is an overestimation of the actual incidence rate because of 3 reasons.

1. Patients were routinely screened for diabetes by means of fasting plasma glucose assessments prior to study entry and were not diagnosed with diabetes. Although fasting plasma glucose assessments are less reliable than performing an OGTT to ascertain nondiabetic status prior to study entry, stating that these patients “must be considered unscreened” seems strange, especially when taking into account that none of the other studies that report on incidence rates in patients treated with



antipsychotic medication did any laboratory assessment to confirm nondiabetic status before study entry.<sup>2-4</sup>

2. A sensitivity analysis was conducted on a subset of patients (N = 240) for whom data on the first year of follow-up were already available and who were not diagnosed with diabetes at the baseline screening. This sensitivity analysis resulted in an even higher incidence rate (4.2%).
3. We have compared the incidence of 3.2% to rates reported in the literature in patients treated with antipsychotic medication, all of which were higher than the incidence rate we reported.<sup>2-4</sup> Dr. Cohen argues that we should have restricted our comparison to the study including only patients with schizophrenia, that of Leslie and Rosenheck.<sup>2</sup> Even if we would have done so, this would not have weakened the argument that it is unlikely that the incidence rate of 3.2% is an overestimation of the actual incidence rate, since the rate reported by Leslie and Rosenheck (4.4%, and indeed not 7.3% as erroneously stated in our article) still is higher than the annual incidence rate of 3.2% we report in our article.

However, the approach of ascertaining nondiabetic status at baseline by means of an OGTT, and prospectively following up the possible development of new-onset diabetes cases by regular OGTT assessments, is a methodologically more valid approach. Therefore, Dr. Cohen argues that the most reliable estimate of the incidence risk is the 4.2% incidence rate found in the sensitivity analysis of 240 patients by using this method. In this, we agree with Dr. Cohen. Nevertheless, a cohort of 240 patients is a relatively small sample to assess the low annual incidence rates typically found for diabetes. We therefore think this incidence rate can best be interpreted in the light of the estimated incidence rate found in the total cohort of our study (3.2%).

In conclusion, as of today, there is not a single study that has used the most optimal methodological approach on a large enough sample to draw firm conclusions on the incidence of diabetes in patients with schizophrenia. Based on the incidence rates reported in the articles of Leslie and Rosenheck<sup>2</sup> and that of ourselves, the incidence rates of diabetes in patients with schizophrenia can be estimated to be around 3% to 5%, which indeed is disturbingly high. We intend to further report on incidence rates in a larger sample of patients with schizophrenia using the most reliable method of ascertaining nondiabetic status at baseline by means of an OGTT and prospectively following up the possible development of new-onset diabetes cases by regular OGTT assessments in due time.

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#### Prolonged QT Associated With an Overdose of Trazodone

**Sir:** QT prolongation, torsades de pointes ventricular tachycardia, and sudden death have been associated with a variety of neuropsychiatric medications, particularly neuroleptics and tricyclic antidepressants.<sup>1</sup> Case reports have documented QT prolongation after overdose with serotonin reuptake inhibitors.<sup>2</sup> Trazodone is an atypical antidepressant that has rarely been associated with QT prolongation in humans,<sup>3-5</sup> although an association has been reported in animals.<sup>6</sup> We present a case of trazodone-induced prolonged QT interval associated with overdose and confirm the relationship between very high trazodone blood levels and QT prolongation.

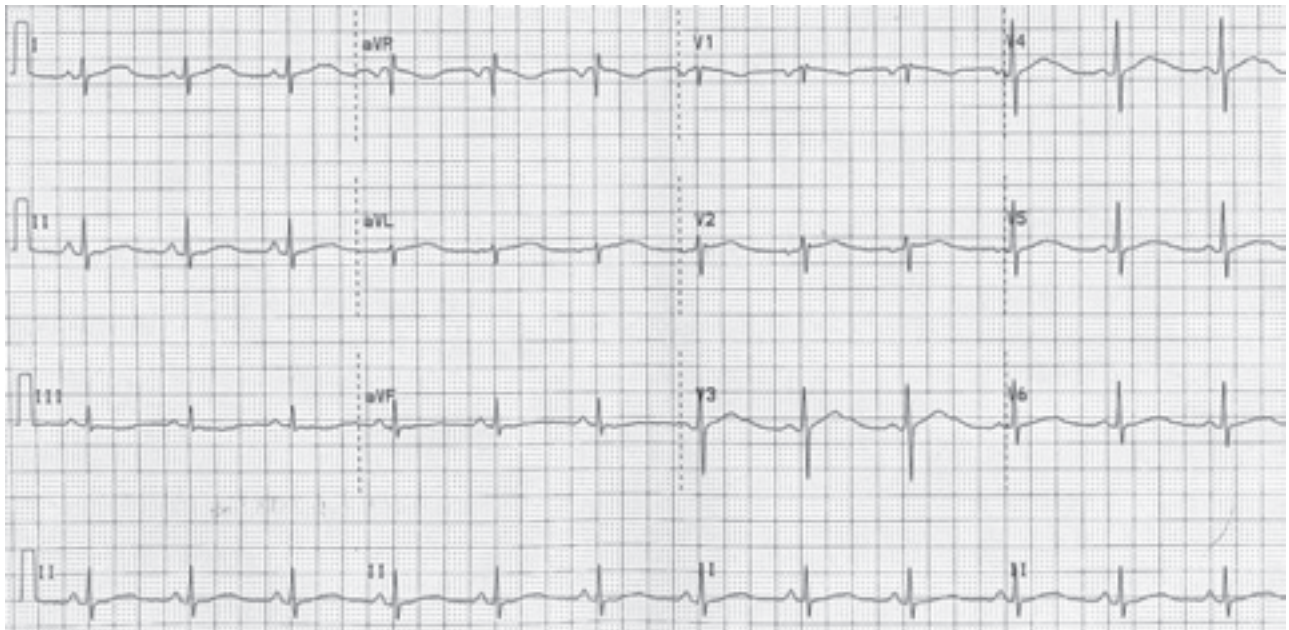
**Case report:** A 36-year-old male with a history of depression, posttraumatic stress disorder, and sarcoidosis was admitted after a self-reported ingestion of 80 tablets of a combination of trazodone and one other drug, which the patient reported to be bupropion and the emergency medical service reported as buspirone, as well as ethanol.

On presentation to the emergency department, the patient was alert and oriented with normal, stable vital signs. Charcoal lavage and intravenous metaclopramide were administered, routine serum laboratory values were drawn, and an electrocardiogram (ECG) was performed. Serum potassium (3.5 mEq/L), magnesium (2.2 mg/dL), thyroid-stimulating hormone (4.19 U/mL), and free T4 (0.99 ng/dL) levels were normal. Chest radiograph showed no cardiomegaly. An echocardiogram taken on the second hospital day showed normal left ventricular size and function (left ventricular ejection fraction of 58%) without evidence of left ventricular hypertrophy.

The initial ECG demonstrated normal sinus rhythm at 74 beats per minute. QT intervals ranged from 440 msec in lead II to 580 msec in leads V<sub>3</sub> and V<sub>4</sub>, with a range of QTc by Bazett's formula of 491 msec to 646 msec using the preceding R-R interval (Figure 1). An ECG obtained 13 hours after admission and subsequent ECGs showed normal QT intervals of approximately 380 msec in leads II and V<sub>3</sub>, with a heart rate of 67 beats per minute (QTc = 414 msec) and resolution of QT dispersion.

A urine toxicology screen was negative for cocaine, benzodiazepines, barbiturates, methadone, and opiates. Serum salicylate, acetaminophen, and dilantin levels were undetectable. The serum ethanol level was 41 mg/dL at admission. Serum samples drawn at admission and 36 hours later were sent to a specialty laboratory for measurement of trazodone, bupropion, and buspirone levels (buspirone was tested only at hour 36 due to insufficient specimen on admission). The patient's admission serum trazodone level was greater than 3000 ug/L (reference range = 750-1600 ug/L); the level was zero at 36 hours. Bupropion was undetectable in both samples, as was buspirone at

Figure 1. Electrocardiogram Taken 3 Hours Following Trazodone Ingestion



hour 36. The patient was asymptomatic and in sinus rhythm throughout the admission.

This is the third reported case associating trazodone ingestion with transient QTc prolongation and the first to verify trazodone ingestion with high serum levels. It is possible the patient concomitantly ingested buspirone, which to our knowledge has not been implicated in QT prolongation. Particularly notable in this case was the remarkable level of QT dispersion on admission, with a difference of 140 msec between leads II and V<sub>3</sub>. QT dispersion may also be a predictor of sudden cardiac death with drug-induced QT prolongation.<sup>7</sup> The risk of sudden or unexplained death with trazodone appears to be small, but cases have been reported with overdoses, particularly when used with other psychiatric medications.<sup>8</sup> Our findings, combined with prior reports, suggest that patients taking trazodone should have ECGs, particularly if they are taking other medications or if they have underlying heart disease (which exaggerates effect of medications that cause QT prolongation<sup>1</sup>). As with several other psychiatric medications,<sup>1,2</sup> the apparently small but definite risk of QT prolongation with high levels of trazodone must be weighed against the benefit of the drug.

*The authors report no financial or other relationships relevant to the subject of this letter.*

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#### Clozapine Interchangeability Issues

**Sir:** In the recent study by Alessi-Severini et al.,<sup>1</sup> the authors present potentially useful data regarding an important medication. Fifty-eight subjects are reported on. This would represent a fraction of the total patients treated with clozapine in Manitoba at the time who underwent a switch. No mention is given of the method of selecting this subset; a systemic bias may be present. The study is retrospective, which limits its utility. As the authors were associated with the University of Manitoba, it may be that the subset of patients they report on received a higher level of care than is standard. The outcome measures used are crude and may miss significant changes in symptoms and functioning. As the authors point out,<sup>1</sup> the literature is divided on the issue of bioequivalence and risk of switch-related decompensations with clozapine. The decompensated clozapine patient often poses a major clinical and health economic challenge.

A significant number of the subjects reported on in the Alessi-Severini et al. study<sup>1</sup> had been taking clozapine for less than 1 year at the time of the switch (28%). One would expect that these patients would have continued to show functional improvement and lower health care utilization in the ensuing 6 months; such was not the case in this study.

Unlike Manitoba, British Columbia has experienced 2 years of "lowest cost alternative" reimbursement for new clozapine starts only, with all patients previously treated with the brand-name version "grandfathered"; in other words, those who were on brand-name clozapine may remain on it. This approach was felt by the British Columbia government to be reasonable in order to reduce the risks inherent in switching between monitoring systems. The British Columbia experience suggests that a multi-provider environment presents caregivers with added challenges and clozapine patients with compounded risks. The monitoring systems of the generics have not, in my opinion, proven consistently reliable. As governments work to deinstitutionalize chronic psychiatric patients, these issues should be considered, because clozapine has unique utility in this patient population.

Psychosis often takes away one's ability to make rational judgments. Persons with psychosis are often fearful that others mean to harm them. They often are ambivalent about their medications. Changing pills, be it the shape, color, or texture, can, in my experience, lead to noncompliance in previously compliant patients.

Clozapine is the only medication in Canada that has mandatory, centralized monitoring as a prerequisite for its use. The monitoring system is complex and involves patients, physicians, mental health care workers, families, and the monitoring system itself. Although the Alessi-Severini et al. study is interesting, it does not, in my opinion, provide a compelling rationale to guide clinical practice.

*Dr. Flynn has acted as a consultant for, has received honoraria from, or has been a member of the speaker/advisory boards for AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Janssen-Ortho, Novartis, Otsuka, and Pfizer. He received no support for this work.*

#### REFERENCE

1. Alessi-Severini S, Honcharik PL, Simpson KD, et al. Evaluation of an interchangeability switch in patients treated with clozapine: a retrospective review. *J Clin Psychiatry* 2006;67:1047-1054

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#### Dr. Alessi-Severini Replies

**Sir:** My colleagues and I appreciate Dr. Flynn's comments on our article<sup>1</sup> and the opportunity to clarify some aspects of our study.

As stated in our article, Canadian provinces have adopted different approaches to clozapine interchangeability according to their particular policies and evaluation processes. British Columbia Pharmacare may apply their "low cost alternative" policy to certain drug categories, but interchangeability is established by the College of Pharmacists. In Manitoba, interchange-

ability, as recommended by the Manitoba Drugs Standard and Therapeutics Committee to the Minister of Health, is translated into legislation and the reimbursement of the low cost alternative automatically applies.

The main objective of our study was to determine whether or not the interchangeability decision was associated with therapeutic problems for patients switched from the brand name to the generic clozapine. The study was prompted by concerns that were voiced at the time of implementation of interchangeability regarding alleged non-bioequivalence of the products, as well as anecdotal reports of patients' decompensation upon switching formulations.

As stated in our article, charts for all outpatients attending the psychiatric clinics at the Health Science Centre in Winnipeg (that serves a diverse urban population) were reviewed. As such, no bias was introduced by sample selection. Inclusion criteria screened only for patients who had been stable on the same dose of clozapine for at least 2 months before the interchangeability switch. This was deemed appropriate in order to reduce variability and eliminate confounding factors in the comparison of formulations. With respect to the comment regarding crude outcomes, it was accepted that in the absence of therapy adjustments, observed variations were not considered to be clinically significant. Given that our study population received consistent monitoring and a high level of care, even slight changes in therapeutic response would have been detected.

We would like to clarify that only 12% of patients had been taking clozapine for less than 1 year at the time of the switch (Table 2 in the article<sup>1</sup>) and, while our study was not powered to evaluate functional improvement and health care use reduction in this population subset, this was observed for 5 of the 7 patients.

Our study was not designed to evaluate the quality of the manufacturers' monitoring programs; however, no comments suggesting problems concerning administrative aspects of the switch were recorded in any patient's chart. Regarding patients' safety, we agree that the existence of multiple monitoring systems has the potential to create difficulties; however, clozapine represents a unique case in which generic substitution will not occur without the knowledge of the prescribing physician who is registered in the monitoring program together with the patient and the pharmacist.

In conclusion, our report makes no pretense at being a clinical practice guideline; however, within the limitations of a retrospective design, it provides the first piece of rigorous evidence, produced without corporate or direct government sponsorship, on the interchangeability of 2 clozapine formulations.

*The principal investigator of this study, Dr. Alessi-Severini, has never received any honoraria and/or consulting fees from either manufacturer of the clozapine formulations evaluated in the study.*

#### REFERENCE

1. Alessi-Severini S, Honcharik PL, Simpson KD, et al. Evaluation of an interchangeability switch in patients treated with clozapine: a retrospective review. *J Clin Psychiatry* 2006;67:1047-1054

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