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Quantifying Intraindividual Variations in Plasma Clozapine Levels: A Population Pharmacokinetic Approach

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ABSTRACT

Objective: Clozapine has strong recommendations for therapeutic drug monitoring. While factors that influence interindividual variation in plasma clozapine levels have been extensively reported, intraindividual variation remains poorly studied. We employed a population pharmacokinetic approach to assess intraindividual variations in plasma levels of both clozapine and *N*-desmethylclozapine, as well as the impact of smoking on this variability.

Methods: Patients who were initiated on clozapine from January 2009 to December 2010 and who provided at least 2 plasma samples were included in this study. The observed concentrations of clozapine and *N*-desmethylclozapine were applied in a Bayesian pharmacokinetic modeling approach by using a previously published pharmacokinetic model from an independent sample to compute a predicted concentration. The predicted concentrations of clozapine and *N*-desmethylclozapine were then compared with the observed concentrations in the form of a ratio: predicted-to-observed concentration ratio (C_{pred}/C_{obs}). The coefficient of variation of the C_{pred}/C_{obs} ratios was taken as a measure of intraindividual variation.

Results: A total of 723 plasma levels from 61 patients were included in this analysis. The coefficient of variation of C_{pred}/C_{obs} ratios for clozapine and *N*-desmethylclozapine were 29.8% (SD = 17.2%) and 27.4% (SD = 16.4%), respectively. Though values were higher, smoking did not have a significant effect on coefficients of variation of clozapine (33.5% vs 26.3%, $P = .184$) or *N*-desmethylclozapine (30.7% vs 24.2%, $P = .100$).

Conclusions: Clinicians need to be aware of intraindividual variability and not assume that plasma levels are static. If plasma levels are used to guide dosing of clozapine, serial measurements rather than a single level might be necessary to make an informed clinical decision. The clinical implications of intraindividual variability in plasma clozapine levels need further study.

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Clozapine has a unique pharmacologic profile and represents the most effective antipsychotic in the treatment of refractory schizophrenia.[1,2] Unfortunately, clozapine's association with agranulocytosis relegates it to a third-line agent with specific indications for use in refractory or treatment-resistant schizophrenia, in addition to patients with recurrent suicidal behaviors.[3,4] Clozapine is one of the few antipsychotics with a strong recommendation for therapeutic drug monitoring in clinical practice[5,6]; several lines of evidence suggest efficacy at plasma clozapine levels ≥ 350 ng/mL.[7–10] As such, interindividual variations in plasma clozapine levels have been extensively studied and the findings relatively well reported. Factors such as age, sex, and dose have each been reported to influence clozapine plasma levels.[11–13] As importantly, factors that induce or inhibit cytochrome P450 enzymes, specifically 1A2 (CYP1A2) and 3A4 (CYP3A4), as well as genetic polymorphisms of P-glycoprotein, a drug transporter present in the gastrointestinal tract, impact plasma levels of clozapine.[14] From these various studies, models have been constructed to aid clinicians in predicting plasma clozapine levels for each individual.[12,15]

Although intraindividual variations in plasma clozapine levels have been reported as early as 1977,[16] it has been relatively understudied. Understanding intraindividual variation is, however, critical to permit dose adjustments in relation to individual level changes. Using a coefficient of variation method, 3 studies[17–19] in the literature reported intraindividual variation of plasma clozapine ranging from 18% to 52.8%. The impact of intraindividual variations on clinical outcomes remains unclear though, and interpretation is hampered by the paucity of studies in this area. One study,[19] for example, found no impact of a large degree of variation (52.8%) on psychopathology, while another investigation[18] reported a variation of greater than 19.8% to be associated with an 11-fold increase in risk of rehospitalization. These 3 studies[17–19] adjusted for clozapine dose and/or weight in their computation of coefficient of variation but did not consider other pertinent parameters, such as dosing frequency, timing of sample collection, and smoking, in the variance.

Cigarette smoking is known to induce CYP1A2, a key metabolizing enzyme converting clozapine to *N*-desmethylclozapine, thereby reducing clozapine levels.[12,20,21] Notably, smoking behaviors have been noted to change over time in conjunction with clozapine use.[22] The quality and quantity of cigarettes smoked, as well as

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degree to which smoke is inhaled, are all factors that might lead to fluctuations in plasma clozapine levels. Indeed, one study[17] found smokers to have larger intraindividual variations of plasma clozapine levels.

The present study aims to quantify the degree of intraindividual variation in plasma clozapine and *N*-desmethylclozapine levels using a ratio of predicted to observed concentration (C_{pred}/C_{obs}). Predicted concentrations were derived using a previously validated population pharmacokinetics model for clozapine in an independent sample.[21] Adopting a population pharmacokinetic approach provides a more precise estimate of the expected plasma level and hence a better evaluation of the observed variation. With regard specifically to cigarette smoking, we hypothesized it would be associated with a greater degree of intraindividual variation.

Clinical Points

- Factors that influence interindividual variation in plasma clozapine levels are often reported, but the degree of intraindividual variation has not been well studied.
- This study found a large degree of intraindividual variation.
- As a consequence of intraindividual variations in plasma clozapine levels, serial measurements rather than a single level might be needed to guide clozapine dose adjustments in clinical practice.

METHODS

Study Setting and Data Collection

Patients were from the Centre for Addiction and Mental Health (CAMH) in Toronto, Canada. Individuals who were initiated on clozapine at CAMH within the study period January 2009 to December 2010 were chosen because of the initiation of electronic medical records in January 2009, permitting more comprehensive data collection. Inclusion criteria for this study included at least 2 eligible plasma clozapine levels performed at the CAMH clinical laboratory. Data regarding age, sex, smoking status, psychiatric diagnoses, and plasma levels were collected from a comprehensive chart review; in addition, prescription data, including nonpsychotropics, were noted. The study was approved by the Research Ethics Board at CAMH.

Plasma Concentrations of Clozapine and *N*-Desmethylclozapine

Concentrations of clozapine and *N*-desmethylclozapine were assayed in heparinized plasma. High-Performance Liquid Chromatography (HPLC; Waters) was used with ultraviolet detection at 245 nm and a limit of quantification of 100 nmol/L. Remoxipride was used as the internal standard. The coefficient of variation was < 5% for both analytes. This was an in-house modification of a previously published method.[23] Plasma samples drawn at steady state (ie, ≥ 7 days after a stable clozapine dose regimen) were considered to be eligible.[1] All plasma clozapine levels performed within 2 years of initiation of clozapine were extracted, and information on clozapine dose as well as dosing regimen was obtained from medical records.

Population Pharmacokinetic Analysis

Population pharmacokinetic analysis was performed on nonlinear mixed-effects modeling software (NONMEM version 7; ICON). The observed clozapine and *N*-desmethylclozapine concentrations were utilized in a nonlinear mixed-effects pharmacokinetic modeling approach using a previously validated pharmacokinetic model from an independent sample drawn from the CAMH.[11,21] In addition to demographic information such as age and sex, data relating to clozapine dose, time of dose, time of plasma sampling, and observed clozapine and *N*-desmethylclozapine concentrations were entered into the model for each sample to generate an empirical Bayes estimate for each individual's pharmacokinetic parameter. These estimates were used to calculate an individual predicted concentration. The predicted clozapine and *N*-desmethylclozapine concentrations were then compared with the observed concentrations in the form of a ratio (C_{pred}/C_{obs}). As this ratio increases beyond a value of 1, it implies that the model has overestimated the plasma concentration. Assuming the applied pharmacokinetic model was adequate, this would imply that the observed plasma level was lower than expected because the patient has not received or absorbed the dose prescribed. Conversely, as the ratio decreases below 1, the model has underestimated the observed concentration, which could be due to the patient having received or absorbed more than the prescribed dose or the clearance of the drug having occurred more slowly than anticipated.

Statistical Analysis

The coefficient of variation represents the degree of variability in relation to the mean and was calculated (standard deviation divided by the mean) for plasma clozapine and *N*-desmethylclozapine levels. A coefficient of variation of the C_{pred}/C_{obs} ratio was calculated for each study participant. After we checked for normality assumptions, either the Student *t* test or Mann-Whitney *U* test was chosen to examine relationships between the coefficient of variation and factors of interest. Spearman ρ correlations were used to examine the degree of agreement between 2 continuous variables. Linear regression was used to investigate the variance in the coefficient of variation explained by smoking. A 2-sided $P < .05$ was considered statistically significant, and all statistical analyses were conducted on IBM SPSS version 20.

RESULTS

Sixty-one of 101 patients initiated on clozapine therapy were included in this study. Of the 40 patients excluded, 13 had no plasma clozapine levels performed, 13 had no information

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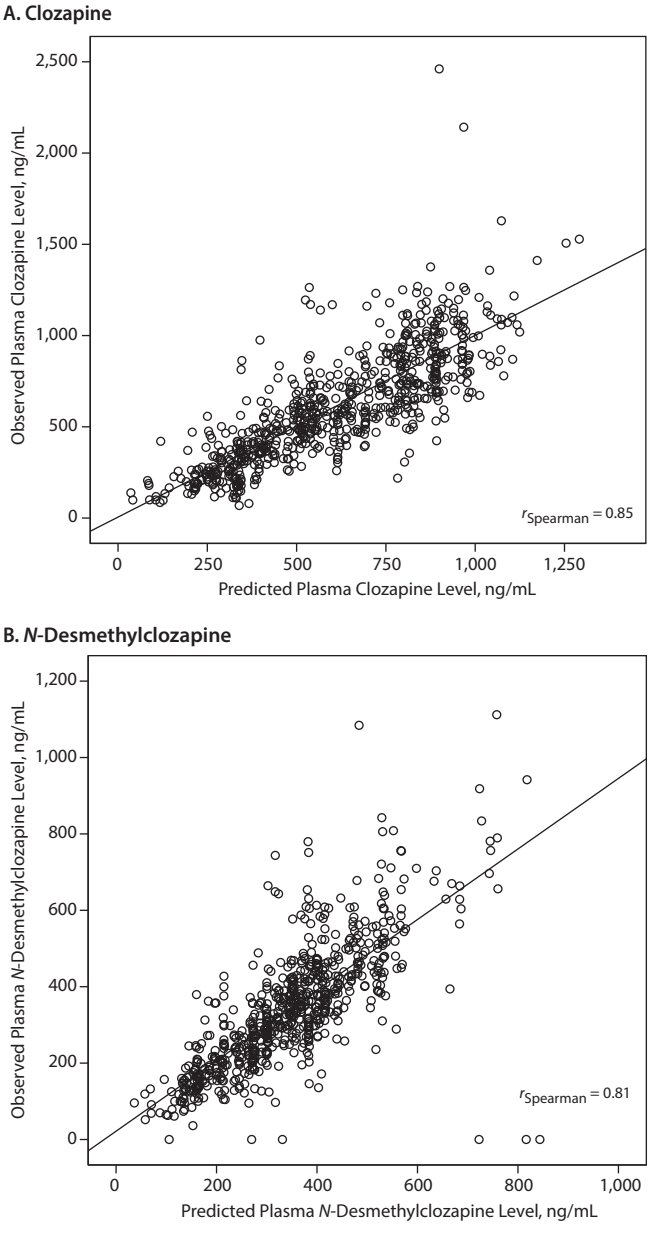
Table 1. Description of Study Sample

Variable	Total Sample	Smoking	Nonsmoking	*P* Value
Sex, n (%)				.178
Male	44 (72.1)	24 (80.0)	20 (64.5)	
Female	17 (27.9)	6 (20.0)	11 (35.5)	
Psychiatric diagnosis, n (%)				.572
Schizophrenia	50 (83.3)	26 (86.7)	25 (80.6)	
Schizoaffective	8 (13.3)	4 (13.3)	4 (12.9)	
Bipolar disorder	1 (1.7)	0	1 (3.2)	
Delusional disorder	1 (1.7)	0	1 (3.2)	
Age, mean (SD), y	36.41 (12.6)	37.1 (13.3)	35.7 (13.3)	.800
Intraindividual coefficient of variation, mean (SD), %				
Clozapine	29.8 (17.2)	33.5 (19.2)	26.3 (14.5)	.184
N-desmethylclozapine	27.4 (16.4)	30.7 (16.7)	24.2 (15.6)	.100

Figure 1. Scatterplots of Observed Versus Model Predicted Plasma Concentrations of (A) Clozapine and (B) *N*-Desmethylclozapine



on time of sampling and/or were not sampled at steady state, and 14 had a single plasma clozapine level. A total of 723 plasma levels were measured on these 61 individuals over the course of 2 years, with a median of 5 plasma levels per patient (range, 2–56). Six *N*-desmethylclozapine levels were below the limits of detection and were excluded from analysis involving *N*-desmethylclozapine. Sample characteristics are reported in Table 1. Thirty of 61 patients (49.2%) were smokers. The ranges of observed plasma clozapine and *N*-desmethylclozapine levels were 68.6–2,461.1 ng/mL and 36.2–1,112.1 ng/mL, respectively.

There were strong correlations between predicted and observed concentrations for both plasma clozapine ($r_{Spearman} = 0.85$, $P < .001$; Figure 1A) and plasma *N*-desmethylclozapine ($r_{Spearman} = 0.81$, $P < .001$; Figure 1B) levels. This is in contrast to the modest correlations obtained between observed concentrations and clozapine doses for plasma clozapine ($r_{Spearman} = 0.20$, $P < .001$) and *N*-desmethylclozapine ($r_{Spearman} = 0.32$, $P < .001$) levels. The mean ± SD C_{pred}/C_{obs} ratios for clozapine and *N*-desmethylclozapine were 1.09 ± 0.40 and 1.08 ± 0.33, respectively.

Intraindividual coefficients of variation ranged from 6.2% to 79.1% for clozapine and 2%–74.2% for *N*-desmethylclozapine. There were no significant correlations between number of samples provided per patient and coefficient of variation for clozapine ($r_{Spearman} = 0.124$, $P = .343$) and *N*-desmethylclozapine ($r_{Spearman} = 0.152$, $P = .243$). Forty-three patients (70.5%) had a coefficient of variation ≥ 19.8%, a level previously shown to be associated with increased risk of rehospitalization.[18] Figure 2 plots the observed and predicted plasma clozapine and *N*-desmethylclozapine levels over time in relation to the prescribed dose for 2 selected male patients. To remove the potential confounding effects of sex, nonadherence, concomitant medications, and self-report of clozapine administration time on plasma clozapine levels, we selected these 2 patients, who were inpatients at the point of clozapine sampling, with little or no change to concomitant medications. Patient A was a nonsmoker and patient B was a smoker. Both were inpatients during the time plasma samples were collected, with no or stable concomitant medications over the sampling period. Medication adherence was strictly supervised by the ward staff. The predicted concentration for plasma clozapine and *N*-desmethylclozapine levels appeared more stable compared to the corresponding observed concentration values. An interesting observation was the gradual decline in both plasma clozapine and *N*-desmethylclozapine levels over time in both patients, more prominent in Figure 2B where the clozapine dose and regimen were unchanged.

Although the intraindividual coefficients of variation of plasma clozapine and *N*-desmethylclozapine appeared higher for smokers compared to nonsmokers, the differences were not statistically significant in our study sample. In line with this, the amount of variance in coefficients of variation explained by smoking status for clozapine ($r^2 = 0.043$) and

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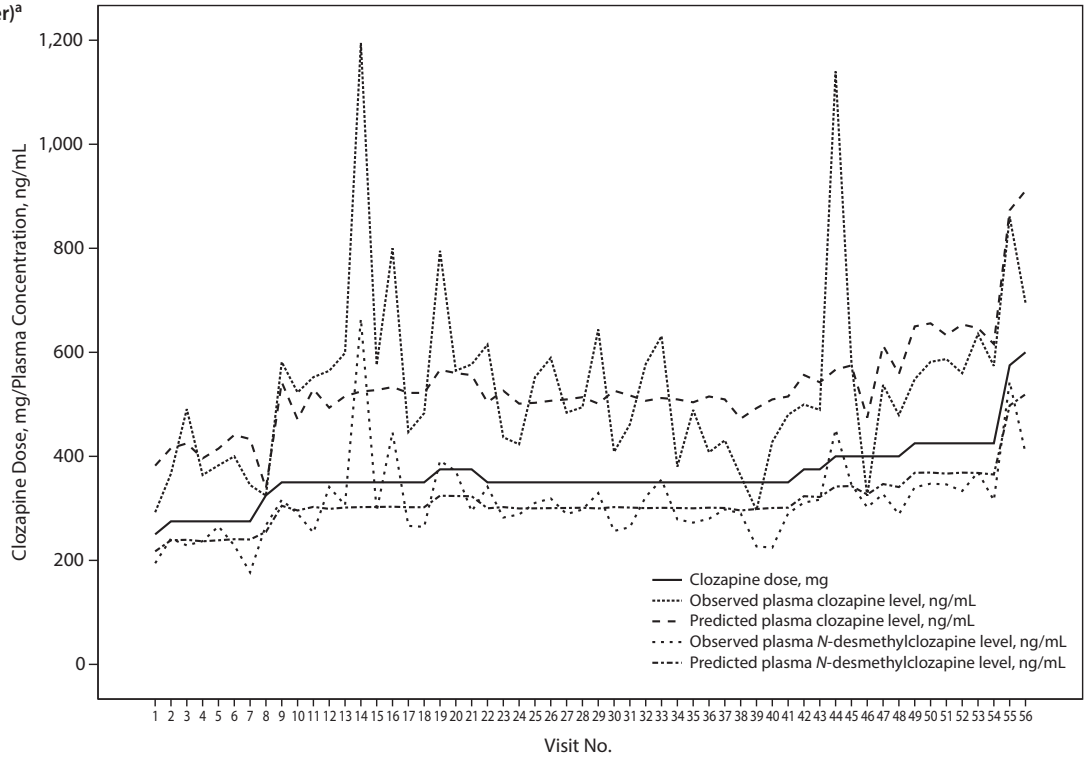
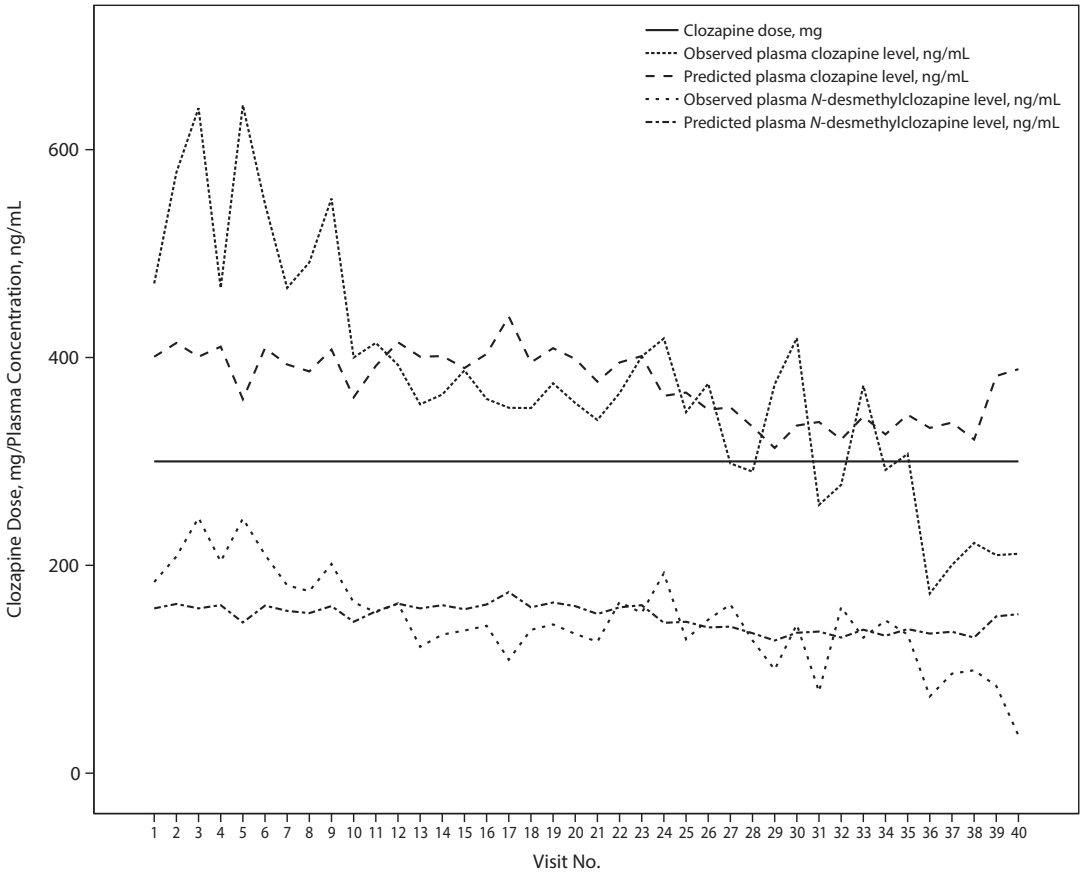
Figure 2. Fluctuations in Observed and Predicted Plasma Clozapine and *N*-Desmethylclozapine Levels for 2 Inpatients[a]

A. Patient A (nonsmoker)[a]



B. Patient B (smoker)[b]



[a]Male inpatient with clozapine dose ranging from 250 to 600 mg, and coefficients of variation of 20.5% and 14.8% for clozapine and *N*-desmethylclozapine, respectively. There were no concomitant medications over the reported time period.
[b]Male inpatient with stable clozapine dose at 300 mg, and coefficients of variation of 29.1% and 50.1% for clozapine and *N*-desmethylclozapine, respectively. The patient had no change in concomitant medications over the plasma sampling period.

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N-desmethylclozapine ($r^2 = 0.040$) was small. When men were compared to women, there were no differences in intraindividual coefficients of variation for plasma clozapine (28.9% [SD = 15.7%] vs 32.3% [SD = 21%], $P = .573$) and *N*-desmethylclozapine (25.2% [SD = 14.3] vs 33% [SD = 20.2%], $P = .161$) levels. Age did not have a significant relationship on coefficients of variation of plasma clozapine ($r_{Spearman} = 0.11$, $P = .382$) and *N*-desmethylclozapine ($r_{Spearman} = 0.10$, $P = .427$) levels.

DISCUSSION

To our knowledge, this study represents the largest of its kind to investigate intraindividual variation in clozapine. We employed a population pharmacokinetic approach and found a sizeable degree of intraindividual variation for both clozapine and *N*-desmethylclozapine levels, which was within the range reported in the literature.[17–19] Age and sex did not appear to be associated with differences in the intraindividual variations.

We detected a medium effect size (Cohen $d = 0.42$) for smoking on coefficient of variation of clozapine, but this finding did not reach statistical significance. Nevertheless, smoking accounted for only a small amount of variance in coefficients of variation of clozapine and *N*-desmethylclozapine. Therefore, other factors of intraindividual variation need to be explored. Patient-related factors such as adherence are likely to be a key determinant of variation, bearing in mind that medication nonadherence is not an "all or none" outcome but occurs along a continuum that can vary over time.[24,25] Furthermore, a certain degree of inaccuracies in self-reported clozapine intake timings can be expected. Other patient-related factors such as brief, time-limited concomitant medications or supplements might alter the pharmacokinetics of clozapine, leading to the observed variability. There was no information as to the formulation of clozapine prescribed and whether tablets were crushed prior to ingestion. All these drug-related factors can affect absorption of the drug and, therefore, the observed plasma levels.[26]

Diet is another significant factor that could influence bioavailability of clozapine, contributing to intraindividual variability. In the case of clozapine, caffeine would stand out as the most-studied dietary substance[27]; however, contradictory findings exist with respect to its impact on clozapine plasma levels. Caffeine is metabolized by CYP1A2, although reports[28,29] of its effect on CYP1A2 activity are conflicting. While different investigations[15,30] have found that caffeine intake reduces clozapine levels, there are also reports[29,31] suggesting increased clozapine levels. Other potential dietary factors include grapefruit and grape juices in addition to cruciferous vegetables, all of which have been known to alter CYP1A2 activity. Furthermore, fruit juices have been shown to inhibit P-glycoprotein, thereby reducing absorption of clozapine.[28] Unfortunately, in this investigation, dietary information was unavailable for the study participants.

Findings from the present study have important clinical ramifications. First, the results call into question the clinical utility of clozapine therapeutic drug monitoring. Can clinicians reliably make clozapine dose adjustments after a single plasma level, or do they require a series of levels in order to make a better-informed decision? This issue has been raised in studies of other medications, including olanzapine[32] as well as human immunodeficiency virus (HIV) medications,[33,34] and clearly has implications in how clozapine therapeutic drug monitoring is conducted in clinical settings. Awareness of variability appears important, with evidence that greater intraindividual variability in clozapine levels is associated with adverse clinical outcomes such as relapse[35] and rehospitalization.[18] Outside psychiatry, similar clinical observations have been made with immunosuppressive agents in organ transplantation and with antiretrovirals in HIV.[34,36]

Another pertinent observation from the present data was a gradual decline in plasma clozapine levels over time, as illustrated in Figure 2. The same observation was made in a previous study[19] where plasma levels were noted to decrease over 12 weeks despite individuals being on stable clozapine doses. Authors of that study surmised that this could be due to enzyme induction by clozapine, as elevated liver enzymes have been observed soon after clozapine exposure; however, this hypothesis requires further examination. Clozapine is not known to be an inducer of CYP1A2, and drug-metabolizing activity is reportedly reduced in hepatitis.[37] Furthermore, plasma levels of both clozapine and *N*-desmethylclozapine declined, as shown in Figure 2, suggesting that CYP1A2 activity was not increased. It is also possible that the activities of other metabolic pathways for clozapine are up-regulated, or absorption of clozapine affected, over time. A gradual decline in medication adherence remains another possibility; we are reminded that medication adherence may fluctuate over time.[38,39] Clearly, further research along these lines is required given that clozapine therapeutic drug monitoring is currently advocated and utilized routinely in clinical decision making regarding clozapine dosing.

One of the strengths of this study is the "real-world" clinical setting in which plasma samples were collected, which, in this way, is reflective of data clinicians would receive in practice settings. Further, the single-site examination of all study samples employed here reduces the impact of measurement bias. Adopting a previously validated population pharmacokinetic model also provides a more precise estimate of expected plasma clozapine and *N*-desmethylclozapine levels. This is evident in Figure 1 and from the strength of the correlations between predicted and observed concentrations. At the same time, there are limitations to note. There was no specific information on medication adherence and caffeine intake, both of which could contribute to the variability seen. Given this, plasma levels of 2 inpatients in whom medication adherence was strictly supervised still demonstrated large intraindividual variations; thus, the observed variability cannot be fully

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explained by nonadherence alone. We were also unable to factor in concomitant medications that might interact with clozapine in the model. Smoking in this study was recorded as a dichotomous variable and at baseline only. It is possible that patterns of smoking changed over the time period examined, although it is unlikely that it was stopped; there is evidence that smoking cessation rates of patients with schizophrenia are even lower than those reported in the general population.[40,41] Furthermore, it was the intent of this study to examine the effect of variability in smoking behaviors on plasma clozapine levels. Outcome data pertaining to adverse events and efficacy were unavailable for the present study, limiting our examination of the impact of observed intraindividual variability.

In conclusion, we found notable intraindividual variability in plasma levels of clozapine and *N*-desmethylclozapine. Clinicians need to be cognizant of this and not assume that plasma levels are static. If clozapine therapeutic drug monitoring is being used to guide dosing, serial measurements, rather than a single level, will better inform clinical decision making. At the same time, there is a need to better understand factors influencing levels, an example being the noted decline in plasma clozapine levels over time and mechanisms underlying this phenomenon.

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Drug names: clozapine (Clozaril, FazaClo, and others), olanzapine (Zyprexa and others).

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