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RESEARCH ARTICLE

Differences in clozapine metabolism across geographical regions in Turkiye

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ABSTRACT

Objective: The efficacy of clozapine is influenced by the pharmacogenetics of its metabolism, which can vary significantly among individuals. This study investigates regional variations in serum clozapine and norclozapine levels across Turkiye.

Method: A retrospective analysis was conducted on 1,428 serum clozapine measurements from 328 patients treated at Hacettepe University Department of Psychiatry between 2014 and 2022. Patients were categorized based on their birthplaces and residential addresses into seven geographical regions of Turkiye. Serum levels of clozapine and norclozapine were measured, and clozapine/norclozapine ratios were calculated. Linear mixed models were used to assess the effects of region, age, sex, and clozapine dose on therapeutic drug monitoring outcomes.

Results: Significant regional differences were observed in serum norclozapine levels, with notably lower levels in the Eastern Anatolia Region (β=-179.04, SE=49.7). No significant regional differences were found in serum clozapine levels or clozapine/norclozapine ratios. Age (p=0.004) and clozapine dose (p<0.001) were positively associated with norclozapine levels, while sex showed no significant association.

Conclusion: This study highlights inter-regional differences in clozapine metabolism within Turkiye, suggesting that regional factors may play a role in clozapine pharmacokinetics. These findings indicate that clozapine metabolism is influenced not only by genetic variability but also by a complex relationship of sociocultural factors. The results support the need for more personalized approaches to clozapine dosing and monitoring to enhance treatment efficacy, safety, and tolerability.

Keywords: Clozapine, geographical variations, norclozapine, schizophrenia spectrum disorders therapeutic drug monitoring, Turkiye

INTRODUCTION

Clozapine is considered the gold standard among second-generation antipsychotic drugs for the treatment of treatment-resistant schizophrenia (1). Due to its narrow therapeutic index and dose- or concentration-related side-effects, therapeutic drug monitoring (TDM) is essential for individualized dose optimization (2, 3). Although the therapeutic plasma concentration range of clozapine is typically set between 350–600 ng/mL, substantial inter-individual variability is frequently observed in clinical practice (2, 4). Recent evidence linking rapid clozapine titration to serious adverse effects such as myocarditis

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and pneumonia has prompted increased interest in understanding the determinants of clozapine metabolism (5). As a result, there has been a shift away from uniform titration protocols and fixed-dose regimens toward more personalized treatment approaches. These strategies emphasize slower titration and individualized dosing based on the features of clozapine metabolism (6, 7).

Clozapine is primarily metabolized in the liver by the CYP1A2 enzyme, with norclozapine (N-desmethylclozapine) being its major metabolite (3). Variations in CYP1A2 activity, influenced by genetic background, significantly impact clozapine metabolism (7). International guidelines recommend lower clozapine doses for individuals of Asian descent due to their generally lower CYP1A2 activity (7). Recent reports from Japan and Korea have indicated a higher incidence of myocarditis, pneumonia, and clozapine-associated inflammation with standard titration protocols, suggesting that individuals of Asian ancestry require lower therapeutic doses compared to those of European ancestry (8–10). These findings highlight the need for substantial revisions to the clozapine package insert to account for regional differences in metabolism (6). However, studying the genetic underpinnings of clozapine metabolism remains challenging, even though interethnic variations in clozapine metabolism are largely attributed to genetic or epigenetic factors, such as CYP polymorphisms (7). Moreover, current commercial kits for detecting CYP1A2 polymorphisms are insufficient to capture many of the common variants associated with clozapine metabolism (7).

In addition to genetic factors, individual patient characteristics and environmental influences also play significant roles in clozapine metabolism. Well-established covariates affecting clozapine pharmacokinetics include CYP450 polymorphisms, sex, age, and smoking status (4), while environmental factors such as diet, medication adherence, and co-prescriptions further contribute to variability. A population-based pharmacokinetic study by Wills et al. (11) demonstrated associations between clozapine levels and variables such as body weight, age, sex, and CYP activity through multiple linear regression analysis. However, a population TDM model developed using these covariates accounted for only 5% of the observed variability in plasma concentrations within the same population (11). This discrepancy between predicted and observed concentrations underscores the potential influence of additional, unaccounted-for environmental factors on clozapine metabolism.

From the perspective of human-environment interaction, the places and conditions in which individuals are born, grow, and live are considered social determinants of health outcomes (12). In this context, the term "exposomic health geography" has been proposed to describe the relationship between biological mechanisms and geographical locations (13). This approach conceptualizes geographical locations as potential biological or chemical exposures, while still accounting for underlying biological processes. It emphasizes interpreting geographical characteristics within their broader sociocultural and political contexts (12). Although a wide range of clozapine concentrations has been reported across different countries (4), TDM of clozapine is not routinely implemented in Turkiye, and inter-individual differences are under-investigated. To the best of our knowledge, no large-scale study has yet examined regional variations in clozapine and norclozapine concentrations within Turkiye, and such regional differences remain unexplored. To address this gap, the present study aims to evaluate clozapine TDM and investigate regional differences in clozapine metabolism across Turkiye.

METHODS

Study Participants

Individuals receiving clozapine treatment for a diagnosis of schizophrenia (F20.X), schizoaffective disorder (F25.X), other psychotic disorders, unspecified psychosis (F28.X-29.X), or bipolar affective disorder (F30.X-31.X) according to International Classification of Diseases, 10th Revision (ICD-10) criteria (14), and who had serum clozapine measurements between January 1, 2014 and December 31, 2022, were included in the study. Data were collected from the inpatient and outpatient clinics of the Hacettepe University Department of Psychiatry. All participants were aged 18 years or older. Exclusion criteria included incomplete data on birthplace or residential address, a diagnosis of Parkinson's disease, or the presence of severe uncontrolled medical conditions that could confound clozapine dosing decisions, such as severe neutropenia or myocarditis.

Participants' birthplaces and residential addresses were determined through retrospective chart review. These were categorized into one of the seven geographical regions of Turkiye: Mediterranean, Eastern Anatolia, Aegean, Southeastern Anatolia, Central Anatolia, Black Sea, and Marmara Regions.

Ethics approval for the study was obtained from the Hacettepe University Ethics Committee (Approval No:

Table 1: Baseline characteristics of the sample

Variable	Number of patients=328 Number of measurements=1,428
Sex, female, n (%)	145 (44%)
Duration of clozapine treatment, years, mean±SD	8.1±7.0
Age, years, mean±SD	40.3±12.2
Clozapine dose, mg, mean±SD	348.2±192.9
Clozapine level, ng/mL, mean±SD	678.7±450.4
Norclozapine level, ng/mL, mean±SD	304.3±189.0
Clozapine/norclozapine ratio, mean±SD	2.5±1.2

n: Number; SD: Standard deviation.

GO21/994, Date: 16/08/2024). Because participants' data were obtained anonymously without accessible personal identifying information and electronic records and files were retrospectively reviewed by the researchers, informed consent was not applicable. The study was conducted in accordance with the latest version of the Declaration of Helsinki.

Assessment of Therapeutic Drug Monitoring Characteristics

Serum clozapine and norclozapine levels were retrospectively obtained from patients' electronic medical records. Patients' characteristics, including sex, age, and clozapine dose at the time of each measurement, were recorded. To ensure accuracy, all patient charts and electronic records were reviewed by two researchers. Norclozapine/clozapine ratios were calculated manually.

Therapeutic drug monitoring was not a routine practice at our center between 2014 and 2022. Serum clozapine levels were typically measured in cases of suspected adverse effects or following changes in clozapine dosage. The minimum and maximum number of measurements per patient, as well as the number of patients with at least two measurements, are presented in the Results section to provide further context regarding TDM practices.

Serum samples were collected immediately before the morning dose (through level), 12 hours after the last dose. Clozapine and norclozapine levels were analyzed using high-performance liquid chromatography (HPLC) at the Hacettepe University Hospital Central Laboratory, in accordance with routine clinical monitoring procedures.

Statistical Analysis

Categorical variables were presented as numbers and frequencies, while continuous variables were expressed as means±standard deviations. Relationships between TDM variables and geographical regions were examined using linear mixed models. The dependent variables included clozapine levels, norclozapine levels, and clozapine/norclozapine ratios. Independent variables were defined as age, sex, clozapine dose, and the distribution of birthplaces and residential addresses across Turkiye's geographical regions. When a significant association between TDM variables and geographical regions was identified, binary comparisons between regions were conducted using estimated marginal means with Tukey's adjustment. Statistical analyses were performed using R software, and a p value of <0.05 was considered statistically significant.

RESULTS

Over the eight-year study period, a total of 1,428 serum clozapine level measurements from 328 patients were included (Table 1). Of the participants, 56% (n=183) were male. The mean duration of clozapine treatment was 8.1±7.0 years. At the time of the baseline measurements, the mean patient age was 40.3±12.2 years, and the mean clozapine dose at the time of TDM measurement was 348.2±192.9 mg/day. The mean clozapine level was 678.7±450.4 ng/mL, while the mean norclozapine level was 304.3±189.0 ng/mL. The mean clozapine/norclozapine ratio was 2.5±1.2. The minimum number of measurements per patient was 1 (observed in 82 patients), while the maximum was 25, recorded in three patients. Notably, 75% of patients (n=246) had at least two clozapine and norclozapine level measurements.

The distribution of participants' birthplaces across the geographical regions of Turkiye was as follows: Mediterranean Region 4% (n=14), Eastern Anatolia Region 6% (n=21), Aegean Region 3% (n=11), Southeastern Anatolia Region 3% (n=9), Central Anatolia Region 68% (n=222), Black Sea Region 12% (n=40), and Marmara Region 3% (n=11). The distribution of

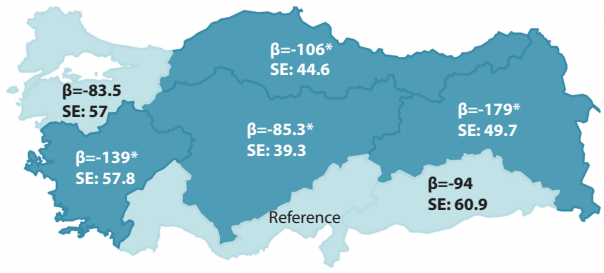

Figure 1. Linear mixed model analysis of norclozapine levels by birthplaces, adjusted for age, sex, and clozapine dose. Dark shaded areas indicate statistical significance.
*p<0.05; β: Estimate of fixed effect; SE: Standard error.

measurements by geographical regions of Turkiye was as follows: Mediterranean Region 4% (n=51), Eastern Anatolia Region 6% (n=79), Aegean Region 4% (n=51), Southeastern Anatolia Region 2% (n=34), Central Anatolia Region 69% (n=992), Black Sea Region 11% (n=162), and Marmara Region 4% (n=59). Linear mixed model analysis revealed that lower norclozapine levels were significantly associated with the Eastern Anatolia, Aegean, Central Anatolia, and Black Sea Regions, after adjusting for age, sex, and clozapine dose (Fig. 1, Table 2). Among the controlled variables, older age (β=1.84, SE=0.64, p=0.004) and higher clozapine doses (β=0.46, SE=0.03, p<0.001) were associated with higher norclozapine levels, whereas sex showed no significant association (β=-11.36, SE=16.35, p=0.48).

Post-hoc binary comparisons of norclozapine levels between regions showed a significant difference between the Mediterranean Region and the Eastern Anatolia Region (β=179.04, SE=49.7, p=0.007) (Table 3). Other binary comparisons did not yield statistically significant differences.

The linear mixed model did not reveal a significant association between geographical regions and clozapine levels or clozapine/norclozapine ratios after controlling for age, sex, and clozapine dose. No significant associations were found between the distribution of residential addresses and clozapine levels, norclozapine levels, or clozapine/norclozapine ratios in the linear mixed models adjusted for age, sex, and clozapine dose.

DISCUSSION

This study demonstrated that serum norclozapine levels varied across the geographical regions of Turkiye, with particularly lower levels observed in individuals whose birthplaces were in the Eastern Anatolia Region. In contrast, clozapine levels and clozapine/norclozapine ratios were consistent across regions, based on participants' birthplaces. Additionally, no associations were observed between residential addresses and clozapine TDM levels.

The observed geographical variations in norclozapine levels may be attributed to two primary factors: 1) Ethnic or genetic variations in CYP1A2 activity, and 2) Regional sociocultural factors influencing drug metabolism. Firstly, the lower norclozapine levels in the Eastern Anatolia Region may reflect underlying ethnolinguistic diversity in Turkiye (15), suggesting a potential higher prevalence of the poor metabolizer phenotype for CYP1A2 in this population subgroup. However, the clozapine/norclozapine ratio is considered an indicator of CYP1A2 activity (11, 16), despite some conflicting reports in the literature (17). A ratio greater than 1.5 reflects reduced CYP1A2 activity, while a ratio

Table 2: Linear mixed model analysis of birthplaces and norclozapine levels*

	β	SE	t	p
Eastern Anatolia Region	-179.04	49.7	-3.603	<**0.001**
Aegean Region	-138.97	57.8	-2.402	**0.017**
Southeastern Anatolia Region	-94.05	60.9	-1.546	0.123
Central Anatolia Region	-85.31	39.3	-2.171	**0.031**
Black Sea Region	-105.96	44.6	-2.378	**0.018**
Marmara Region	-83.48	57.0	-1.464	0.144
Mediterranean Region	Reference			
Clozapine dose	0.46	0.03	13.910	<**0.001**
Age	1.84	0.64	2.855	**0.004**
Sex (male)	-11.36	16.4	-0.695	0.484

*Dependent variable: Norclozapine level. Independent variables: Birthplace (region), clozapine dose, age, and sex. β: Estimate; SE: Standard error. Statistical significance set at 0.05 (bold values).

Table 3: Post-hoc binary comparisons of norclozapine levels across geographical regions

	β	SE	t	p*
Mediterranean Region vs. Eastern Anatolia Region	179.04	49.7	3.601	**0.01**
Mediterranean Region vs. Aegean Region	138.97	57.9	2.401	0.20
Mediterranean Region vs. Southeastern Anatolia Region	94.05	60.9	1.545	0.72
Mediterranean Region vs. Central Anatolia Region	85.31	39.3	2.170	0.32
Mediterranean Region vs. Black Sea Region	105.96	44.6	2.377	0.21
Mediterranean Region vs. Marmara Region	83.48	57.0	1.464	0.77
Eastern Anatolia Region vs. Aegean Region	-40.07	54.0	-0.741	0.99
Eastern Anatolia Region vs. Southeastern Anatolia Region	-84.99	57.2	-1.487	0.75
Eastern Anatolia Region vs. Central Anatolia Region	-93.73	33.3	-2.817	0.08
Eastern Anatolia Region vs. Black Sea Region	-73.08	39.6	-1.845	0.52
Eastern Anatolia Region vs. Marmara Region	-95.56	53.1	-1.800	0.55
Aegean Region vs. Southeastern Anatolia Region	-44.92	64.4	-0.698	0.99
Aegean Region vs. Central Anatolia Region	-53.66	44.5	-1.207	0.89
Aegean Region vs. Black Sea Region	-33.01	49.1	-0.673	0.99
Aegean Region vs. Marmara Region	-55.49	60.7	-0.914	0.97
Southeastern Anatolia Region vs. Central Anatolia Region	-8.73	48.5	-0.180	1.00
Southeastern Anatolia Region vs. Black Sea Region	11.92	52.8	0.226	1.00
Southeastern Anatolia Region vs. Marmara Region	-10.57	63.7	-0.166	1.00
Central Anatolia Region vs. Black Sea Region	20.65	25.2	0.820	0.98
Central Anatolia Region vs. Marmara Region	-1.84	43.6	-0.042	1.00
Black Sea Region vs. Marmara Region	-22.49	48.3	-0.465	0.99

β: Estimate; SE: Standard error. *p values adjusted using Tukey's method. Statistical significance set at 0.05 (bold values).

exceeding 2 indicates CYP1A2 saturation (16). In our study, clozapine/norclozapine ratios were similar across the geographical regions, which weakens the hypothesis of an ethnic or genetic variation in CYP enzymes specific to the Eastern Anatolia region.

Secondly, sociocultural factors, such as medication adherence and accessibility of healthcare services, may also explain the lower norclozapine levels in Eastern Anatolia. Despite our finding of a mean clozapine/norclozapine ratio of 2.5, consistent with previous literature (reported range: 1.2–3.4) (17), ratios above 2 may also suggest chronic poor adherence to clozapine treatment (18). Reinitiating clozapine after a period of non-adherence leads to an increased clozapine/norclozapine ratio, while recent non-adherence leads to a lower ratio, as norclozapine has a longer half-life than clozapine (11, 18). Lower norclozapine levels may also be influenced by other factors such as smoking status, obesity, and/or co-administration of inhibitory drugs (7, 11, 19, 20). Smoking induces CYP1A2 activity, leading to faster clozapine metabolism and increases clearance of both clozapine and norclozapine (18, 21). In Turkiye, smoking rates are generally comparable across geographical regions, with the exception of the Black Sea Region, where rates are slightly lower (22). On the other hand, obesity is associated with nearly two-fold higher clozapine and norclozapine levels due to its impact on CYP1A2 activity (5, 19, 23). A national epidemiological study reported that the obesity rate in Eastern Anatolia was slightly lower compared to other regions (22). However, these smoking and obesity rates were not specific to psychiatric populations. We are unable to make further comments due to missing information regarding smoking status, obesity rates, and co-prescriptions.

From a social perspective, applying standard dose adjustments without considering patient-specific characteristics, such as genetic background, medication adherence, and smoking status, may lead to inequalities and suboptimal treatment outcomes (24). Dose individualization based on a multifactorial approach that includes both biological and sociodemographic covariates may enhance population pharmacokinetic modeling (11, 24). Our

findings suggested that individual differences in clozapine metabolism require further investigation, and that a single standard dosing strategy may be insufficient for our country.

Our linear mixed model analysis revealed no significant regional differences in clozapine levels. As mentioned above, norclozapine has a longer half-life than clozapine. Clozapine levels show a considerable variation throughout the day and are strongly influenced by dose skipping, nonadherence, and drug-drug interactions (4, 16, 18). These factors may contribute to the absence of significant findings for clozapine levels, in contrast to the significant regional variations observed in norclozapine levels.

We found that age was positively associated with norclozapine levels. Increased plasma levels of clozapine and norclozapine with age have been well-documented in the literature (4, 25, 26). The clearance of both clozapine and norclozapine decreases after the age of 39 (25). Population pharmacokinetic models based on large sample sizes have estimated that a dose reduction of 20–56% between the ages of 20 and 80 is needed to achieve effective plasma levels (18, 26). However, this is a neglected topic, as there are no clear recommendations for dose adjustments in elderly patients undergoing clozapine treatment (27).

Our findings indicated no association between sex and the TDM parameters, although females have lower CYP1A2 activity than males (28). Current evidence suggests that females have higher dose-adjusted clozapine levels and require lower doses to reach the targeted serum level compared to males (4, 7, 18, 25, 29). Similarly, increased norclozapine levels have been reported in females (21, 30). However, several studies have found no significant sex differences in clozapine and norclozapine levels (27, 29, 31, 32). These conflicting findings may be attributed to small sample sizes or variability in ethnic backgrounds.

The retrospective design was the primary limitation of this study, compounded by the absence of a formal scale to assess treatment adherence and the lack of data on smoking status and co-prescriptions. Additionally, the distribution of patients across regions was uneven, with the majority of the sample consisting of patients from the Central Anatolia region. Nevertheless, the large sample size and adjustments for clozapine dose and sex strengthen our findings. Moreover, the consideration of geographical regions based on both birthplace and residential address provided a novel social context for our findings, which has often been overlooked in the existing literature.

CONCLUSION

In conclusion, this study demonstrates differences in clozapine metabolism across various geographical regions in Turkiye, revealing significant variations in serum norclozapine levels that may be influenced by genetic and sociocultural factors. Notably, individuals from the Eastern Anatolia Region exhibited lower norclozapine levels, suggesting potential regional disparities in clozapine metabolism. Although clozapine/norclozapine ratios remained consistent, indicating no major discrepancies in CYP1A2 activity across regions, the findings underscore the importance of considering both regional and individual variations when optimizing clozapine therapy. Addressing these differences through tailored pharmacokinetic modeling that incorporates both biological and sociodemographic factors could significantly improve treatment outcomes and reduce disparities. Our findings support a more individualized approach to clozapine dosing, suggesting that standardized dosing may not be suitable for all populations, especially in a country with such diverse regional characteristics as Turkiye. Further research is needed to explore the underlying causes of these regional differences.

Contribution Categories		Author Initials
Category 1	Concept/Design	E.M.
	Data acquisition	I.B., S.O., M.F.I.
	Data analysis/Interpretation	E.M., S.C.G.
Category 2	Drafting manuscript	E.M., S.O., M.F.I.
	Critical revision of manuscript	I.B., N.Y., K.D., A.E.A.Y.
Category 3	Final approval and accountability	E.M., S.O., M.F.I., I.B., N.Y., K.D., S.C.G., A.E.A.Y.
	Supervision	K.D., A.E.A.Y.

Ethical Approval: The Hacettepe University Ethics Committee granted approval for this study (date: 16.08.2024, number: GO21/994).

Conflict of Interest: It was declared that A.E.A.Y. participated in advisory boards and received speaker's fees from Janssen, Abdi İbrahim, Sanovel, Nobel, Adeka, Santa Farma, and Abdi İbrahim Otsuka, and has received support for attending meetings from Janssen in the past year. Other authors declared that they have no conflict of interest.

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