

## ORIGINAL ARTICLE

# A population pharmacokinetic model to guide clozapine dose selection, based on age, sex, ethnicity, body weight and smoking status

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**Aims:** Guidance on clozapine dosing in treatment-resistant schizophrenia is based largely on data from White young adult males. This study aimed to investigate the pharmacokinetic profiles of clozapine and *N*-desmethylclozapine (norclozapine) across the age range, accounting for sex, ethnicity, smoking status and body weight.

**Methods:** A population pharmacokinetic model, implemented in Monolix, that linked plasma clozapine and norclozapine via a metabolic rate constant, was used to analyse data from a clozapine therapeutic drug monitoring service, 1993–2017.

**Results:** There were 17 787 measurements from 5960 patients (4315 male) aged 18–86 years. The estimated clozapine plasma clearance was reduced from 20.2 to 12.0 L h<sup>-1</sup> between 20 and 80 years. Model-based dose predictions to attain a predose plasma clozapine concentration of 0.35 mg L<sup>-1</sup> was 275 (90% prediction interval 125, 625) mg day<sup>-1</sup> in nonsmoking, White males weighing 70 kg and aged 40 years. The corresponding predicted dose was increased by 30% in smokers, decreased by 18% in females, and was 10% higher and 14% lower in otherwise analogous Afro-Caribbean and Asian patients, respectively. Overall, the predicted dose decreased by 56% between 20 and 80 years.

**Conclusion:** The large sample size and wide age range of the patients studied allowed precise estimation of dose requirements to attain predose clozapine concentration of 0.35 mg L<sup>-1</sup>. The analysis was, however, limited by the absence of data on clinical outcome and future studies are required to determine optimal predose concentrations specifically in those aged over 65 years.

## KEYWORDS

age, clozapine, dose requirement, ethnicity, population pharmacokinetics, treatment-refractory schizophrenia, sex, therapeutic drug monitoring

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## 1 | INTRODUCTION

### 1.1 | Clozapine in treatment-refractory schizophrenia

Clozapine has unique efficacy in treatment-refractory schizophrenia<sup>1</sup> and, at doses 10–30% of those used in schizophrenia, Parkinson disease psychosis.<sup>2</sup> However, the drug is under-utilized in those aged over 65 years due to concerns about adverse effects, including agranulocytosis, constipation, hypersalivation, hypotension, myocarditis, pneumonia, sedation and tachycardia.<sup>3</sup> An additional barrier to initiating treatment, and one that has recently been questioned,<sup>4</sup> is the need for intensive safety monitoring, including weekly monitoring of white cell count for the first 18 weeks, fortnightly for the next 34 weeks and monthly thereafter. Consensus guidance, which is largely based on data from White young adult males suggests that most, but not all, people with treatment refractory schizophrenia show a moderate/good response to clozapine at predose (trough) clozapine plasma concentrations between 0.35 and 0.6 mg L<sup>-1</sup>, but there is considerable variation in response and adverse effects,<sup>5</sup> and others have proposed a range between 0.25 and 0.42 mg L<sup>-1</sup>.<sup>6–8</sup>

### 1.2 | Clozapine pharmacokinetics

Clozapine undergoes almost complete absorption, has oral bioavailability between 27 and 47% due to highly variable first pass metabolism<sup>9</sup> and is 95% bound to plasma proteins. The time to achieve peak concentration is around 2.5 h following oral dosing.<sup>10–12</sup> Clozapine undergoes extensive metabolism and demethylation via cytochrome P (CYP) 1A2 and to a lesser extent CYP3A4, to form the major plasma metabolite *N*-desmethylclozapine (norclozapine).<sup>13</sup>

Plasma concentrations of clozapine and norclozapine for a given dose vary widely both between and within individuals. This is partly explained by factors that either activate, or inhibit CYP1A2, including exposure to cigarette smoke (polycyclic aromatic hydrocarbons induce CYP1A2), caffeine (CYP1A2 substrate),<sup>14</sup> female sex (oestrogen inhibits CYP1A2) and Asian ancestry, which is associated with lower CYP1A2 activity compared to other ethnic groups.<sup>15</sup>

The contribution of norclozapine to treatment response has not been clearly established, but several studies have shown an association between norclozapine plasma concentration and side effects (sedation, hypersalivation and possibly seizures).<sup>16</sup> As a result, routine therapeutic drug monitoring (TDM) of both is recommended.<sup>17,18</sup>

### 1.3 | Clozapine in older people

There is no clear guidance on the clozapine dose adjustment required for patients with schizophrenia or other forms of psychosis aged 65 years and above.<sup>19</sup> One survey of TDM data reported plasma clozapine concentrations of 0.53 ± 0.33 mg L<sup>-1</sup> following doses of 150–250 mg day<sup>-1</sup> in those aged over 65 years.<sup>19</sup>

#### What is already known about this subject

- Clozapine dosage guidance in treatment-resistant schizophrenia is largely based on young White men.
- Clozapine plasma clearance is affected by sex, ethnicity, smoking status and body weight, amongst other factors.
- Pharmacokinetic studies have observed inconsistent effects of age on plasma clozapine clearance but were limited by small sample sizes.

#### What this study adds

- There was a significant age-related reduction in clozapine clearance in male and female smokers and nonsmokers of all ethnicities.
- Clozapine dose requirements to attain a predose plasma concentration of 0.35 mg L<sup>-1</sup> decreased by 56% between 20 and 80 years.
- Future studies that combine pharmacokinetic and clinical outcome data are required to ascertain optimal predose plasma concentrations in patients aged >65 years.

Population pharmacokinetic studies, which use a mixed effects based approach to estimate pharmacokinetic parameters, have however produced inconsistent findings.<sup>20</sup> This may be partly explained by small sample size ( $n = 13–391$ ), or differences in factors such as body weight, concomitant medication and smoking status (smoking is less prevalent in those aged over 65 years).<sup>19</sup> This study aimed to develop a population pharmacokinetic model for clozapine and norclozapine using information from a large TDM dataset, with the following aims:

- 1) To investigate the effect of age on clozapine dose–concentration relationships, after accounting for repeated sampling and covariates (sex, ethnicity, body weight and smoking status).
- 2) To use model-based estimates to predict the doses required in male and female White, Afro-Caribbean and Asian smokers and nonsmokers aged between 20 and 80 years to attain a predose plasma clozapine concentration of 0.35 mg L<sup>-1</sup> on repeated dosing.

## 2 | METHODS

### 2.1 | Data source

We studied anonymised data from the analyses of blood samples (use of EDTA anticoagulant requested) submitted for clozapine

TDM from patients from the UK and Ireland, November 1993–December 2017. Patient samples that had been referred during investigation of: (i) death during clozapine treatment; (ii) suspected self-poisoning requiring medical admission, for example, via a hospital Emergency Department; and (iii) suspected clozapine exposure in neonates were excluded where these could be identified. Use of the data was approved by Guy's Research Ethics Committee reference 05/Q0704/158. Details of the assay are described in Supplementary File 1.

Only samples for which daily dose (mg, tablet form), date and time of last dose, date and time of the sample, plasma clozapine and norclozapine concentration ( $\text{mg L}^{-1}$ ), age (years), sex, ethnicity, smoking status and body weight (kg) were available were studied. Samples were excluded if plasma clozapine concentrations were below the limit of assay sensitivity ( $0.01 \text{ mg L}^{-1}$ ,  $100 \mu\text{L}$  sample) or were coprescribed medication that may affect clozapine pharmacokinetics (fluvoxamine, paroxetine, fluoxetine, phenytoin, carbamazepine, phenobarbital, sodium valproate and omeprazole).<sup>21</sup>

## 2.2 | Pharmacokinetic model development

A pharmacokinetic model that accounted for the metabolism of plasma clozapine to norclozapine was used to explore sources of variability in dose-concentration relationships. Several approaches to model development were studied (MLXTRAN command files, equations and outputs detailed in Supplementary File 1): 1)  $V/F_{\text{norclozapine}}$  was fixed relative to a metabolic rate constant  $k_m$ <sup>22</sup>; 2)  $V/F_{\text{clozapine}}$  and  $V/F_{\text{norclozapine}}$  were estimated and  $k_f$ , the fraction of  $V/F_{\text{clozapine}}$  converted to  $V/F_{\text{norclozapine}}$ , was fixed to a value of 0.66<sup>23</sup>; 3)  $V/F_{\text{clozapine}}$  was fixed to a value of  $750 \text{ L}$ <sup>24</sup> based on a multiple dosing bioequivalence study that estimated the mean value of  $V/F_{\text{clozapine}}$  for a person of  $70 \text{ kg}$ <sup>25</sup>; 4) The assumption that  $V/F_{\text{clozapine}}$  and  $V/F_{\text{norclozapine}}$  were equal.<sup>26</sup>

The chosen model included the following parameters: (i) clozapine first-order absorption rate constant ( $k_a$ ) fixed at  $0.69 \text{ h}^{-1}$ ; (ii) apparent volume of distribution of clozapine ( $V/F_{\text{clozapine}}$ ); (iii) apparent plasma clearance of clozapine ( $CL/F_{\text{clozapine}}$ ); (iv) metabolic rate constant ( $k_m$ ); (v) apparent volume of distribution of norclozapine ( $V/F_{\text{norclozapine}}$ ), which was assumed to be equal to  $V/F_{\text{clozapine}}$ ; and (vi) apparent plasma clearance of norclozapine ( $CL/F_{\text{norclozapine}}$ ). The term  $F$  represents, here, the bioavailability of the drug that cannot be estimated from oral data alone.

The analysis estimated average parameter (or fixed effect,  $\mu$ ) values in the population, interindividual variability (IIV) of the random effects  $\eta$ , capturing the deviation of each individual parameter from the population average value, and the residual variability ( $\sigma$ ; system noise, dosage history errors). Model development was carried out in Monolix (version 2020R1; [www.lixoft.eu](http://www.lixoft.eu)). Fixed effects, interindividual standard deviation ( $\omega$ ) of the random effects and residual standard deviation were estimated using the stochastic approximation expectation maximization algorithm.<sup>27</sup> IIV was modelled using an exponential model  $\phi_i = \mu \times e^{\eta_i}$ , where  $\phi_i$  and  $\eta_i$  are the individual parameter estimate and corresponding random effect for the  $i^{\text{th}}$  individual. For the

sake of interpretability, the coefficient of interindividual variation was derived using the following approximation:  $\text{sqrt}(e^{\omega^2}) - 1$ .<sup>28</sup>

A combined additive and proportional residual error model ( $y_{ij} = \hat{y}_{ij} + (\sigma_{\text{inter}} + \sigma_{\text{slope}} \cdot \hat{y}_{ij})\varepsilon_{ij}$ ) was used to describe residual unexplained variability, where  $y_{ij}$  and  $\hat{y}_{ij}$  represent the  $j^{\text{th}}$  observed clozapine (or norclozapine) concentration of the  $i^{\text{th}}$  subject, and its corresponding model predicted concentration;  $\varepsilon_{ij}$  is assumed to be normally distributed with a mean of 0 and a variance of 1. Residual errors were estimated separately for clozapine and norclozapine. The most parsimonious structural and statistical models were selected based on the Bayesian information criteria (BIC) that penalizes the likelihood by the number of estimated parameters and the study sample size. An assumption was made that 50% of the daily dose was administered every 12 h. Smoking status, age and body weight were incorporated into the model as time-dependent covariates. Sex and ethnicity were included as categorical covariates.

The base model accounted for differences in body weight, but included no other covariates: Apparent clearance parameters were standardized to  $70 \text{ kg}$  weight, to the power 0.75 (i.e., for an individual  $i$  weighing  $80 \text{ kg}$ ,  $CL/F_{\text{clozapine } i} = \mu CL/F_{\text{clozapine}} \cdot (80/70)^{0.75}$ ); and apparent volume of distribution parameters were standardized to  $70 \text{ kg}$  to the power 1 ( $V/F_{\text{clozapine } i} = \mu V/F_{\text{clozapine}} \cdot (80/70)^1$ ).<sup>29</sup>

Age effects were explored using both linear and exponential functions. Covariates were selected using the Wald test, which compares the ratio of the estimated  $\beta$  value for a covariate divided by its standard error (SE) to a Gaussian distribution. Models were evaluated using goodness-of-fit criteria (SE, BIC), including diagnostic scatter plots (observed vs. predicted concentrations using fixed effects and individual parameter estimates), visual predictive checks (credibility intervals around model predicted time-concentration percentiles overlaid to observed percentiles) and change in IIV.

## 2.3 | Model predictions

Plasma terminal half-life ( $t_{1/2}$ ) was calculated as the ratio of  $\log^2$  and the slope of elimination, which was derived from parameters estimates of apparent clearance and volume of distribution for individuals of  $70 \text{ kg}$  weight.

$$t_{1/2} \text{ clozapine} = \log^2 / k, \text{ where } k = k_e + k_m \text{ and } k_e = (CL/F_{\text{clozapine}}) / (V/F_{\text{clozapine}}).$$

$$t_{1/2} \text{ norclozapine} = \log^2 / k_{\text{em}}, \text{ where } k_{\text{em}} = (CL/F_{\text{norclozapine}}) / (V/F_{\text{norclozapine}}).$$

Model-based estimates of  $V/F_{\text{clozapine}}$ ,  $CL/F_{\text{clozapine}}$ ,  $k_m$  and their SE were used to predict the daily dose required to obtain predose plasma clozapine concentration ( $C_{\text{predose target}}$ )  $0.35 \text{ mg L}^{-1}$ , along with the corresponding 95% confidence interval (CI) of the parameter estimate in White male and female, smokers and nonsmokers aged 20 to 80 years. The following R code was used,

assuming 12 h dosing,  $k_a = 0.69 \text{ h}^{-1}$  and  $\mu$  parameter values for  $V/F_{\text{clozapine}}$ ,  $CL/F_{\text{clozapine}}$  and  $k_m$ :

$$C_{\text{predose\_target}} < -\text{function}(x, k_a, V/F_{\text{clozapine}}, k, \text{target}) x^* k_a / \\ (V/F_{\text{clozapine}} * [k_a - k]) * (\exp(-k * 12) / (1 - \exp(-k * 12))) \\ - \exp(-k_a * 12) / (1 - \exp(-k_a * 12))) - \text{target}.$$

The 95% CIs were calculated by inserting in the code above the upper and lower limits of each parameter using the parameter estimate ( $\hat{\cdot}$ ) and SE (i.e., lower CI =  $\widehat{CL/F_{\text{clozapine}}} * 1.96 - SE$ , higher CI =  $\widehat{CL/F_{\text{clozapine}}} * 1.96 + SE$ ).

The R function uniroot was used to obtain the dose (variable  $x$  in the code below) for which the difference between the model prediction and the target value is null:

```
Uniroot(f = C_trough_target, interval = c[0, 1500], k_a = 0.69, V/F_clozapine
= V, k = k, target = 0.35)$root * 2uniroot
(f = C_trough_target, interval = c[0, 1500], k_a = 0.69, V/F_clozapine
= V_higher, k = k_higher, target = 0.35)$root * 2uniroot
(f = C_trough_target, interval = c[0, 1500], k_a = 0.69, V/F_clozapine
= V_lower, k = k_lower, target = 0.35)$root * 2.
```

## 2.4 | Model-based simulation

Model-based estimates of  $V/F_{\text{clozapine}}$ ,  $CL/F_{\text{clozapine}}$  and  $k_m$  and IIV of these estimates were used to predict the average dose and its 90% prediction interval in the population, by sampling 100 individuals in the parameter population distribution and using uniroot to estimate their target doses, for the following: male/female, smoker/nonsmoker, White, Afro-Caribbean or Asian ethnicity, aged 40 and 80 years. Dose calculations were rounded to the nearest 25 mg to reflect real world prescribing.

## 3 | RESULTS

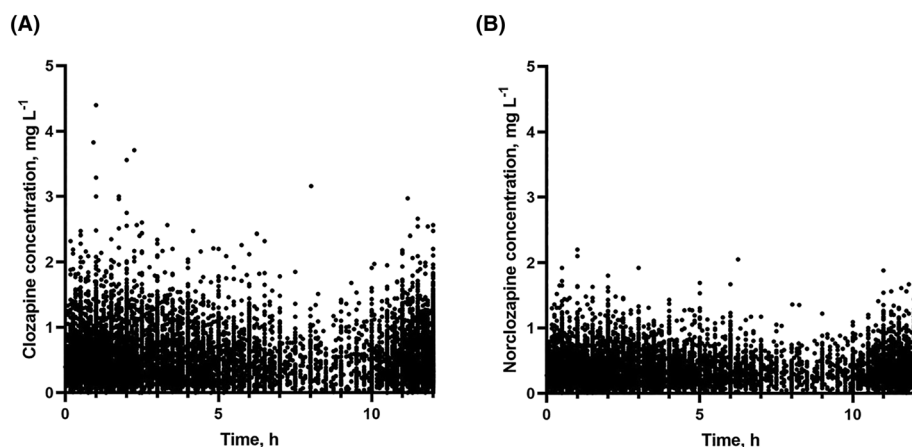
### 3.1 | Base and final pharmacokinetic model

Of 21 761 samples from 7451 patients extracted from the dataset, the following were excluded on the basis of concomitant medication ( $n = 3466$ ; 52 fluvoxamine, 56 fluoxetine, 588 paroxetine, 1840 sodium valproate, 835 omeprazole, 35 phenytoin, 60 carbamazepine), mixed ethnicity ( $n = 377$ ), or plasma clozapine below the limit of assay quantification ( $n = 131$ ). The analysis thus included 17 787 samples (Figure 1) from 5960 patients (4315 male, 1645 female; Table 1).

The base model (Table 2) estimated  $V/F_{\text{clozapine}}$ ,  $CL/F_{\text{clozapine}}$ ,  $k_m$  and  $CL/F_{\text{norclozapine}}$  with excellent precision (relative SE <1% for all parameters). The model explained 60% of the variability in observed plasma clozapine and 69% of the variability in observed plasma norclozapine. IIV was 12, 93, 10 and 7% for  $V/F_{\text{clozapine}}$ ,  $CL/F_{\text{clozapine}}$ ,  $k_m$  and  $CL/F_{\text{norclozapine}}$ , respectively.

Covariate effects on  $CL/F_{\text{clozapine}}$  (Table 2) were significant ( $P < .001$  for all) for smoking status ( $\beta_{\text{Smoker}} CL/F_{\text{clozapine}} = +0.37$ , SE 0.012), sex ( $\beta_{\text{Female}} CL/F_{\text{clozapine}} = -0.24$ , SE 0.021), age ( $\beta_{\text{Age}} CL/F_{\text{clozapine}} = -0.013$ , SE 0.00057) and ethnicity ( $\beta_{\text{Afro-Caribbean}} CL/F_{\text{clozapine}} = +0.12$ , SE 0.035;  $\beta_{\text{Asian}} CL/F_{\text{clozapine}} = -0.19$ , SE 0.041). There was no significant effect of any covariate on  $k_m$  or  $CL/F_{\text{norclozapine}}$ . Incorporation of covariates into the base model reduced the IIV of  $CL/F_{\text{clozapine}}$  from 93 to 82% and BIC was reduced from  $-22\,024$  to  $-23\,587$ . The final model explained 61% of the variability in observed plasma clozapine and 69% of the variability in observed plasma norclozapine. The shrinkages for the variances of the interindividual random effects were 87, 15, 80 and 95% for  $V/F_{\text{clozapine}}$ ,  $CL/F_{\text{clozapine}}$ ,  $k_m$  and  $CL/F_{\text{norclozapine}}$  respectively. The shrinkages for the standard deviation of the residual unexplained variability were 7 and 10% for clozapine and norclozapine, respectively. Covariate model development and the final model parameter estimates (relative SE) are shown in Table 2.

For the reference group (male, age 40 years, 70 kg weight, White, nonsmoker), model estimates of  $CL/F_{\text{clozapine}}$ ,  $k_m$ ,  $V/F_{\text{clozapine}}$  and  $t_{1/2}$  were  $20.2 \text{ L h}^{-1}$ ,  $0.005 \text{ h}^{-1}$ ,  $1460 \text{ L}$  and  $36 \text{ h}$ , respectively. Model



**FIGURE 1** Scatterplot showing the frequency and distribution of sampling times across the dosage interval for (A) clozapine and (B) norclozapine. Each circle represents a sample.

**TABLE 1** Descriptive data (median, 10th, 90th percentiles).

	Male (4315 patients, 13 084 samples)	Female (1645 patients, 4703 samples)
Ethnicity (White/Afro-Caribbean/Asian)	3743 (11 426)/344 (980)/228 (678)	1415 (4069)/113 (308)/117 (326)
Age (year) <sup>†</sup>	36 (25, 52)	40 (26, 57)
Body weight (kg) <sup>†</sup>	87 (67, 115)	80 (58, 108)
Dose (mg/day) <sup>†</sup>	450 (250, 700)	400 (200, 625)
Smoker (%) <sup>†</sup>	8743 (66.8)	2580 (54.9)
Plasma clozapine (mg L <sup>-1</sup> )	0.41 (0.16, 0.91)	0.50 (0.18, 1.1)
Plasma norclozapine (mg L <sup>-1</sup> )	0.30 (0.13, 0.61)	0.34 (0.14, 0.69)
Plasma clozapine:norclozapine ratio	1.4 (0.8, 2.2)	1.5 (0.9, 2.3)
Time of sample after last dose (h)	3.5 (0.7, 11.9)	3.3 (0.6, 11.7)
Samples per patient	2 (1, 5)	2 (1, 5)

<sup>†</sup>At date of sample.

estimates for  $CL/F_{\text{norclozapine}}$  and  $t_{1/2}$  were 12.0 L h<sup>-1</sup> and 69 h respectively.

Covariate effects were used to calculate  $CL/F_{\text{clozapine}}$  for individual  $i$  using the formula:  $CL/F_{\text{clozapine}i} = \mu CL/F_{\text{clozapine}} * (\text{weight}/70)^{0.75} * (\text{age}_i - 40)^{0.013} * (1 + 0.37 \text{ if Smoker}) * (1 - 0.24 \text{ if Female}) * (1 + 0.12 \text{ if Afro-Caribbean}) * (1 - 0.19 \text{ if Asian})$ .

Age-related model predicted reductions in  $CL/F_{\text{clozapine}}$  accounting for its estimation error are shown in Figure 2 for the average White male and female smoker and nonsmoker.

Exploratory analyses were carried out to ascertain if there was an interaction between smoking and covariates. There was no effect of age ( $\beta_{\text{Smoker}} CL/F_{\text{clozapine}} = +0.39$  and  $+0.37$  in those aged below or above 40 years respectively), or sex ( $\beta_{\text{Smoker}} CL/F_{\text{clozapine}} = +0.38$  for males and females); and although there were differences in the effect of smoking based on ethnicity ( $\beta_{\text{Smoker}} CL/F_{\text{clozapine}} + 0.39$ ,  $+0.15$  and  $+0.28$  in White, Afro-Caribbean and Asian ethnicity respectively, this did not improve the model fit (Supplementary File 1, Table 1). Further analyses were carried out to investigate the effects of concomitant medications on  $CL/F_{\text{clozapine}}$  in the larger dataset. Although the predictions were in the expected direction (see Supplementary File 1, Table 2), IIV in  $CL/F_{\text{clozapine}}$  increased from 82 to 98%, with no reduction in residual unexplained variability.

### 3.2 | Dose prediction

The predicted dose to attain a predose steady-state plasma clozapine concentration of 0.35 mg L<sup>-1</sup> was 275 mg day<sup>-1</sup> in the reference group (nonsmoking White male, 70 kg, age 40 years). The corresponding doses were 10% higher and 14% lower in otherwise analogous Afro-Caribbean and Asian patients, respectively. In all cases, the predicted dose was increased by 30% in smokers and decreased by 17% in females (Table 3). The predicted dose decreased by 56% between age 20 and 80 years, all other factors being equal. This decrease is illustrated in Figure 3 for the average White male and female smoker and nonsmoker, accounting for the estimation error of the model parameters. The average predicted dose and 90% prediction intervals

to achieve a predose plasma clozapine concentration of 0.35 mg L<sup>-1</sup> are shown in Table 3 for male and female, White, Afro-Caribbean and Asian smokers and nonsmokers aged 40 and 80 years.

## 4 | DISCUSSION

### 4.1 | Age-related changes in clozapine pharmacokinetics

Guiding dose prediction in older people has been described as ‘a minefield without a map’,<sup>30</sup> reflecting the relative lack of pharmacokinetic data on those aged over 65 years.<sup>31</sup> In this analysis of data collected during routine clinical practice there was a significant effect of age on  $CL/F_{\text{clozapine}}$  that was not accounted for by differences in sex, ethnicity, body weight or smoking status. These findings may be explained by age-related reduction in hepatic metabolism due to reduced liver size and hepatic blood flow<sup>32</sup> and lower CYP activity.<sup>33,34</sup> Other factors, such as physical comorbidities and polypharmacy, which are common in older people with serious mental illness, are beyond the scope of this analysis, but also need to be considered as they may have contributed to the greater heterogeneity in  $CL/F_{\text{clozapine}}$  observed with increasing age.<sup>33</sup> Our estimate of the effect of age on clozapine dosing is higher than in our recently published audit, based on data from a much larger sample from the TDM dataset that predicted a 1.7% decrease in clozapine dose requirements for every 5 years above 40 years.<sup>35</sup> It is, however, consistent with the 4% decrease in dose for every 5 years above 40 years reported by Rostami-Hodjegan and colleagues.<sup>36</sup>

### 4.2 | Smoking status, sex and ethnicity

The effect of cigarette smoking on plasma clozapine clearance is well established and close monitoring of patients with plasma concentrations at the higher end of the target range (>0.6 mg L<sup>-1</sup>) is advised if smoking is stopped either through choice, or due to a change in accommodation (nonsmoking policies), or inability to smoke due to

TABLE 2 Population pharmacokinetic models for clozapine and norclozapine.

Parameters	Base model		Smoke CL/ $F_{\text{clozapine}}$		Sex CL/ $F_{\text{clozapine}}$		Age exp CL/ $F_{\text{clozapine}}$		Ethnic CL/ $F_{\text{clozapine}}$	
	Parameter estimates	Relative standard error (%)	Parameter estimates	Relative standard error (%)	Parameter estimates	Relative standard error (%)	Parameter estimates	Relative standard error (%)	Parameter estimates	Relative standard error (%)
$K_a$ ( $\text{h}^{-1}$ ; fixed)	0.69	ne	0.69	ne	0.69	ne	0.69	ne	0.69	ne
$V/F_{\text{clozapine}}$ (L)	1430	0.5	1390	0.5	1370	0.5	1410	0.4	1460	0.4
$\beta$ Weight_V/ $F_{\text{clozapine}}$	1.0	ne	1.0	ne	1.0	ne	1.0	ne	1.0	ne
$CL/F_{\text{clozapine}}$ ( $\text{L h}^{-1}$ )	23.2	1.1	18.7	1.1	20.3	1.2	19.3	1.3	20.2	1.3
$\beta$ Weight_CL/ $F_{\text{clozapine}}$	0.75	ne	0.75	ne	0.75	ne	0.75	ne	0.75	ne
$K_m$ ( $\text{h}^{-1}$ )	0.006	0.4	0.006	0.4	0.006	0.4	0.006	0.5	0.005	0.5
$\beta$ Smoking_CL/ $F_{\text{clozapine}}$	-	-	+0.40	3.0	+0.39	3.1	+0.39	3.2	+0.37	3.1
$\beta$ Female_CL/ $F_{\text{clozapine}}$	-	-	-	-	-0.28	7.5	-0.26	8.5	-0.24	8.8
$\beta$ Age_CL/ $F_{\text{clozapine}}$ (exponential)	-	-	-	-	-	-	-0.013	4.7	-0.013	4.4
$\beta$ Afro-Caribbean_CL/ $F_{\text{clozapine}}$	-	-	-	-	-	-	-	-	+0.12	30.5
$\beta$ Asian_CL/ $F_{\text{clozapine}}$	-	-	-	-	-	-	-	-	-0.19	21.4
$\beta$ Weight_V/ $F_{\text{norclozapine}}$	1	ne	1	ne	1	ne	1	ne	1	ne
$CL/F_{\text{norclozapine}}$ ( $\text{L h}^{-1}$ )	12.1	0.3	12.0	0.3	11.9	0.3	12.7	0.3	12.0	0.3
$\beta$ Weight_CL/ $F_{\text{norclozapine}}$	0.75	ne	0.75	ne	0.75	ne	0.75	ne	0.75	ne
Inter-individual standard deviation										
$\omega_{\text{V}}/F_{\text{clozapine}}$	0.12	3.4	0.12	3.4	0.12	3.2	0.10	3.5	0.11	3.4
$\omega_{\text{CL}}/F_{\text{clozapine}}$	0.79	1.0	0.74	1.1	0.72	1.1	0.75	1.1	0.72	1.1
$\omega_{\text{K}_m}$	0.10	3.5	0.09	3.3	0.09	3.2	0.13	3.0	0.12	3.1
$\omega_{\text{CL}}/F_{\text{norclozapine}}$	0.07	3.4	0.07	3.8	0.06	3.5	0.07	3.8	0.06	3.9
Residual unexplained standard deviation										
$\sigma_{\text{intercept Clozapine}}$ ( $\text{mg L}^{-1}$ )	0.02	17.8	0.02	17.2	0.02	14.6	0.02	16.2	0.02	15.9
$\sigma_{\text{slope Clozapine}}$	0.40	0.7	0.40	0.7	0.39	0.8	0.39	0.8	0.39	0.7



TABLE 2 (Continued)

Parameters	Base model		Smoke $CL/F_{clozapine}$		Sex $CL/F_{clozapine}$		Age exp $CL/F_{clozapine}$		Ethnic $CL/F_{clozapine}$	
	Parameter estimates	Relative standard error (%)	Parameter estimates	Relative standard error (%)	Parameter estimates	Relative standard error (%)	Parameter estimates	Relative standard error (%)	Parameter estimates	Relative standard error (%)
Fixed effects (unit)										
$\sigma_{intercept}$ Norclozapine ( $mg L^{-1}$ )	0.02	7.6	0.02	7.5	0.02	7.2	0.02	7.2	0.02	7.1
$\sigma_{slope}$ Norclozapine	0.31	0.8	0.31	0.8	0.31	0.8	0.31	0.8	0.31	0.8
Bayesian Information Criteria	-22 024		-22 987		-23 151		-23 389		-23 587	

$K_a$ , first-order absorption rate constant (fixed);  $V/F_{clozapine}$ , apparent volume of distribution of clozapine;  $CL/F_{clozapine}$ , apparent plasma clearance of clozapine;  $k_{tr}$ , metabolic rate constant;  $V/F_{norclozapine}$ , apparent volume of distribution of norclozapine (assumed to be equal to  $V/F_{clozapine}$ );  $CL/F_{norclozapine}$ , apparent plasma clearance of norclozapine;  $\beta$ , covariate effect coefficient;  $\omega$ , standard deviation of interindividual random effects;  $\sigma$ , standard deviation of residual unexplained errors, with intercept ( $mg L^{-1}$ ) and slope (percentage) parameters; ne, not estimated.

physical illness.<sup>37</sup> Our analysis suggested that a 30% increase in dose would be required should someone start smoking in order to maintain an equivalent plasma concentration. This is consistent with the literature<sup>1</sup> and our recent audit.<sup>35</sup>

As in previous studies,<sup>20,35</sup> women had lower clozapine  $CL/F$  than men. These findings were not explained by differences in body weight, but likely reflect sex differences in body composition such as the proportion and distribution of adipose tissue<sup>38</sup> and reduced metabolism due to oestrogen-mediated inhibition of CYP1A2 (premenopausally and possibly through the use of hormone replacement therapy), reduced hepatic blood flow and liver size, and differential expression of other drug metabolizing enzymes.<sup>39</sup>

Ethnicity contributed to variability in  $CL/F_{clozapine}$  (12% higher in Afro-Caribbean, 19% lower in Asian compared to White patients). Differences in body composition, variation in CYP1A2 genetics or epigenetics (heritable changes in gene function that are not explained by DNA sequence, including DNA methylation and histone modifications), or other environmental factors (such as diet) may account for these results, at least in part.<sup>40</sup>

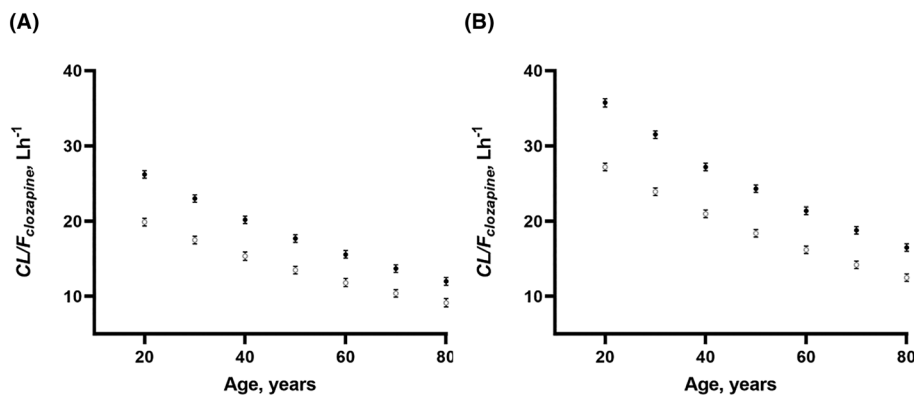
Our dose predictions for White and Asian patients (Table 2) were largely consistent (within 10%) of published recommendations regarding ancestry-based dose adjustments,<sup>15</sup> with the exception of predictions for White female smokers, which were 25% lower in the analysis presented here.<sup>15</sup> Although our dose predictions for those of Asian ethnicity were consistent with our recently published audit, those for White and Afro-Caribbean, male and female, smokers and nonsmokers were consistently lower, but within the 95% CI for each prediction<sup>35</sup> (Supplementary File 1, Table 1).

The finding that dose requirements were increased in Afro-Caribbean patients (Table 3) is in line with the suggestion that dose requirements may be higher in those of African ancestry.<sup>15</sup> Pharmacokinetic studies of olanzapine (also a CYP1A2 substrate) have reported faster clearance in males, smokers and African American patients who participated in the Clinical Antipsychotic Intervention Effectiveness (CATIE) study.<sup>41</sup> In a subsequent analysis of this latter dataset, CYP3A43 genotype rs472660 AA, which is expressed more frequently in those of African ancestry, was associated with faster olanzapine clearance; African ethnicity was no longer significant when this genotype was incorporated in the model.<sup>42</sup> These findings have questioned the relative contribution of CYP3A4 in clozapine metabolism.<sup>43</sup>

In the absence of genetic data, it is unclear to what extent CYP1A2 genotype or environmental factors, including diet, account for the observed ethnic group differences in our analysis. For example, vegetables such as cabbages, cauliflower and broccoli increase CYP1A2 activity<sup>44</sup> and spices that are commonly used in Asian cuisine, such as curcumin (the active component of turmeric) inhibit CYP1A2 activity.<sup>45</sup> It will be important to investigate this in future studies.

### 4.3 | Population pharmacokinetics of clozapine

Published pharmacokinetic models of clozapine have produced wide ranging estimates for  $CL/F_{clozapine}$  (median  $30.3 L h^{-1}$ , range

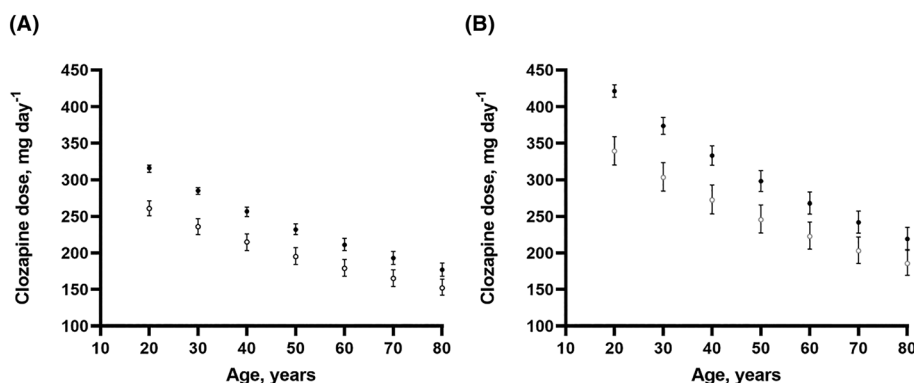


**FIGURE 2** Model-based estimates for clozapine plasma apparent clearance ( $CL/F_{\text{clozapine}}$ ,  $L h^{-1}$ ) and 95% confidence intervals are shown for (A) nonsmoking and (B) smoking White males (black circle) and females (white circle) aged 20–80 years.

**TABLE 3** Predicted dose (90% prediction interval)<sup>†</sup> ( $mg day^{-1}$ ) to achieve predose plasma clozapine of  $0.35 mg L^{-1}$  by sex, ethnicity, age and smoking status.

Age (years)		Male		Female	
		40	80	40	80
Nonsmoker	White	275 (125, 625)	175 (100, 450)	225 (125, 475)	150 (100, 350)
	Afro-Caribbean	300 (125, 800)	200 (100, 500)	250 (125, 550)	175 (100, 375)
	Asian	225 (100, 575)	150 (100, 400)	175 (100, 475)	150 (100, 275)
Smoker	White	375 (150, 850)	225 (100, 775)	300 (125, 825)	175 (100, 350)
	Afro-Caribbean	400 (175, 1050)	250 (125, 975)	325 (150, 975)	225 (100, 450)
	Asian	250 (150, 775)	200 (100, 550)	225 (125, 625)	150 (100, 400)

<sup>†</sup>Dose predictions are rounded to the nearest 25 mg, to reflect real world prescribing. Actual dose predictions are shown in Supplementary File 1.



**FIGURE 3** Predicted dose ( $mg day^{-1}$ ) and 95% confidence intervals to achieve predose plasma clozapine of  $0.35 mg L^{-1}$  are shown for (A) nonsmoking and (B) smoking White males (black circle) and females (white circle) aged 20–80 years.

14.4–45.2) and  $V/F_{\text{clozapine}}$  (median 508 L, range 272–1290), wide IIV in  $CL/F_{\text{clozapine}}$  (median 43%, range 27.1–60.8) and  $V/F_{\text{clozapine}}$  (median 65.7%, range 10–131.5) and inconsistent effects of age.<sup>20</sup> These discrepancies may be partly explained by small sample size and small proportion of samples from patients aged over 65 years. Norclozapine population pharmacokinetics have been evaluated in 6 studies<sup>20</sup>; 4 estimated  $CL/F_{\text{norclozapine}}$  (median  $46.3 L h^{-1}$ , range 32.7–58.9; median IIV 47.2%, range 42.1–60.3); and a single study estimated  $V/F_{\text{norclozapine}}$  (624 L, IIV 75.6%).<sup>23</sup>

The large size and wide age range of individuals in our TDM dataset allowed estimation of pharmacokinetic parameters and covariate effects.<sup>20</sup> Model-based estimates for  $CL/F_{\text{clozapine}}$  ( $20.2 L h^{-1}$ ) are consistent with published models, but  $V/F_{\text{clozapine}}$  was higher (1460 L

than has previously been reported. Estimated clozapine  $t_{1/2}$  was 36 h, consistent with reports that, although  $t_{1/2}$  is 12 h (range 9–17) following a single dose,<sup>46</sup> this increases following repeat dosing.<sup>20,47</sup> Model-based estimates for  $CL/F_{\text{norclozapine}}$  were lower, but  $t_{1/2}$  estimates were consistent with the published data on repeated dosing.<sup>47</sup>

#### 4.4 | Limitations and sources of unexplained variability

This analysis has addressed some of the limitations described in relation to TDM data<sup>48</sup> in that the model accounted for repeated sampling of individuals and was limited to patients for whom dose, age,



date and time of sample, and other relevant information on covariates were available. Moreover, selective analytical methodology quality controlled to international standards was used throughout. It could be argued that clinicians may have been more likely to specify the time since last dose for samples that were not taken predose and this is a possible source of bias in the dataset. This was, however, accounted for in the analysis, as the pharmacokinetic model takes into account time since last dose when exploring dose–concentration relationships and covariate effects. Model-based estimates are then used to simulate and predict predose concentrations.

Although those prescribed either potent CPY1A2 inducers (phenytoin, carbamazepine, phenobarbital), or inhibitors (fluvoxamine) were excluded from the analysis, it is likely that the dataset was incomplete in terms of concomitant medications. Secondly, there was limited information on other factors that could have influenced clozapine metabolism, including caffeine intake, diet, oral contraceptive or hormone replacement therapy use and the presence of inflammation, or of hepatic dysfunction.<sup>16,17,48,49</sup>

It is likely that a proportion of the samples studied here were obtained from patients who were not fully adherent with treatment. Thus, it is possible that plasma clozapine and norclozapine concentrations were underestimated in relation to the prescribed dose in some individuals. It is not possible to fully quantify the influence of nonadherence on clozapine dose individualisation without further modelling of data on clinical outcome, but our  $t_{1/2}$  estimates suggest the drug may be relatively *forgiving* of imperfect adherence, as the duration of effect is likely to exceed the dosage interval.<sup>50</sup>

The possible effect of clozapine-induced gastrointestinal hypomotility on clozapine absorption, and of passive smoking and diet on clozapine dose–concentration relationships are also unknown. Moreover, no account was taken as to the proportion of the prescribed dose that was administered at different times of the day. This is a limitation, as it is likely that a greater proportion of the dose was administered in the evening in many patients.

All of the above factors, together with inaccuracies in relation to the dose or sampling time recorded, may have contributed to the wide IIV and unexplained variability in analyte plasma concentrations. The analysis included a standard scaling factor for body weight, which was important because weight varied considerably across the sample. However, the absence of height information meant that it was not possible to calculate body mass index to assess either the presence, or the extent of obesity.<sup>51</sup>

## 4.5 | Implications

We have produced guidance on the daily dose required to maintain a predose plasma clozapine concentration of  $0.35 \text{ mg L}^{-1}$  across the age range, stratified on the basis of sex, ethnicity and smoking status. Model-based estimates suggested that the dose requirement decreased by approximately 56% between the ages of 20 and 80 years, other factors being equal. This is important because the risk of life-threatening clozapine-induced gastrointestinal hypomotility

and of pneumonia in those prescribed clozapine may not only increase with increasing time on the drug, but may also be related to plasma clozapine concentrations, at least in part.<sup>52,53</sup>

We accounted for the wide between subject variability in our predictions, as our aim was to propose guidance both for the typical individual and the population, based on each of the covariates of interest (age, sex, smoking status and ethnicity). Our choice of a predose concentration of  $0.35 \text{ mg L}^{-1}$  does not take into account possible age-related pharmacodynamic changes, at the neurotransmitter, neuroreceptor or signal transduction level, which may lower optimal predose clozapine concentrations, particularly in those aged over 65 years. Nevertheless, our predictions provide a valuable comparison of the daily dosages needed to reach a prespecified threshold across subgroups.

Future studies should investigate the relationship between plasma clozapine and norclozapine concentrations and clinical outcome specifically in older people, to establish optimal predose plasma clozapine concentrations to achieve efficacy with minimal toxicity and refine dose predictions.

## CONTRIBUTORS

Suzanne Reeves led the study design, carried out data analysis and led on writing the paper; Stephen John Obee carried out data extraction; Julie Bertrand, Samora Hunter and Robert Howard gave input into the study design and analysis plan; Julie Bertrand supervised the analysis of the data and model-based simulations; Robert James Flanagan was responsible for the operation of the clozapine TDM service 1993–2017, initiated the study and contributed to the writing of the paper. All authors approved the submitted manuscript.

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## COMPETING INTERESTS

There are no competing interests.

## DATA AVAILABILITY STATEMENT

Data are available on reasonable request.

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#### SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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