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Rohit Kalra

See next page for additional authors

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Population pharmacokinetics of olanzapine in children

Anil R. Maharaj1 | Huali Wu1 | Kanecia O. Zimmerman1,2 | Julie Autmizguine3 | Rohit Kalra4 | Amira Al-Uzri5 | Catherine M.T. Sherwin6,7 | Stuart L. Goldstein8 | Kevin Watt1,2 | Jinson Erinjeri9 | Elizabeth H. Payne9 | Michael Cohen-Wolkowiez1,2 | Christoph P. Hornik1,2

1Duke Clinical Research Institute, Duke University School of Medicine, Durham, NC, USA
2Department of Pediatrics, Duke University School of Medicine, Durham, NC, USA
3Department of Pediatrics, CHU Sainte-Justine, Montreal, Canada
4Ann & Robert H. Lurie Children’s Hospital of Chicago, Chicago, IL, USA
5Oregon Health and Science University, Portland, OR, USA
6Department of Pharmacotherapy, College of Pharmacy, University of Utah, Salt Lake City, UT, USA
7Department of Pediatrics, Wright State University, Boonshoft School of Medicine, Dayton Children’s Hospital, Dayton, OH, USA
8Department of Pediatrics, University of Cincinnati, Cincinnati, OH, USA
9The Emmes Company, LLC, Rockville, MD, USA

Aims: The aim of this study was to evaluate the population pharmacokinetics (PopPK) of olanzapine in children and devise a model-informed paediatric dosing scheme.

Methods: The PopPK of olanzapine was characterized using opportunistically collected plasma samples from children receiving olanzapine per standard of care for any indication. A nonlinear mixed effect modelling approach was employed for model development using the software NONMEM (v7.4). Simulations from the developed PopPK model were used to devise a paediatric dosing scheme that targeted comparable plasma exposures to adolescents and adults.

Results: Forty-five participants contributed 83 plasma samples towards the analysis. The median (range) postnatal age and body weight of participants were 3.8 years (0.2–19.2) and 14.1 kg (4.2–111.7), respectively. The analysis was restricted to pharmacokinetic (PK) samples collected following enteral administration (oral and feeding tube). A one-compartment model with linear elimination provided an appropriate fit to the data. The final model included the covariates body weight and postmenstrual age (PMA) on apparent olanzapine clearance (CL/F). Typical CL/F and apparent volume of distribution (scaled to 70 kg) were 16.8 L/h (21% RSE) and 663 L (13% RSE), respectively. Developed dosing schemes used weight-normalized doses for children ≤6 months postnatal age or <15 kg and fixed doses for children ≥15 kg.

Conclusion: We developed a paediatric PopPK model for enterally-administered olanzapine. To our knowledge, this analysis is the first study to characterize the PK of olanzapine in participants ranging from infants to adolescents. Body weight and PMA were identified as influential covariates for characterizing developmental changes in olanzapine apparent clearance.

KEYWORDS
children, dosing, olanzapine, paediatric, population pharmacokinetics

1 INTRODUCTION

Use of antipsychotic medications among children has increased dramatically over the last two decades.1–3 This trend is largely driven by use of atypical (second generation) antipsychotics, which represent the most common subtype prescribed to children.4 Despite recent paediatric regulatory approvals in this drug class, approximately two-thirds of atypical antipsychotics prescribed to children are for non-approved
indictions (i.e., off-label). This high prevalence of off-label medication use in children reflects the lack of appropriate safety, efficacy and pharmacokinetic (PK) studies in this population and places children at higher risk of experiencing adverse drug events. Of additional concern is that even when prescribed for labelled indications, children experience some antipsychotic-associated adverse drug events (e.g., sedation and weight gain) more often than adults. Consequently, to promote the safe and effective use of antipsychotics in children, paediatric-focused safety, efficacy and PK investigations are needed.

Olanzapine is a multi-acting receptor-targeted (atypical) antipsychotic that exhibits potent antagonism towards serotonin (5-HT2A, 2C, 5-HT2C), dopamine (D2), histamine (H1) and adrenergic receptors (α1). Based on current US Food and Drug Administration (FDA) approved labelling, olanzapine is indicated for the treatment of schizophrenia and bipolar I disorder (manic or mixed episodes) as a single agent in children ≥13 years; and depressive episodes associated with bipolar I disorder in combination with fluoxetine for children ≥10 years. In addition, olanzapine is administered off-label to children for a myriad of indications including eating, tic, attention-deficit/hyperactivity, autism spectrum and pervasive developmental disorders and delirium. Despite olanzapine’s diverse usage, the relationship between specific PK thresholds (e.g., pre-dose plasma concentrations) and therapeutic efficacy remains ill-defined. Furthermore, few studies exist characterizing the PK of olanzapine in children, especially those <10 years.

In adults, the oral bioavailability of olanzapine is reported to be ≥65%. On average, plasma protein binding is 93% and attributed to both albumin and α-1-acid glycoprotein. Olanzapine is primarily cleared by hepatic metabolism via several enzymes (CYP1A2, CYP2D6, CYP2C8, UGT1A4, and flavin-containing monoxygenase-3), while ~7% of the orally administered dose is excreted unchanged in urine. Previous adult PK investigations indicate that smoking status, sex and race (African American) are significant covariates towards olanzapine apparent oral clearance (CL/F). In adolescents, body weight and sex have been identified as influential covariates. In this study, we sought to evaluate the population pharmacokinetics (PopPK) of olanzapine in children (infants to adolescents) and characterize covariates that contribute towards its PK variability. In addition, using the developed PopPK model, we aimed to devise a model-informed paediatric dosing strategy.

What is already known about this subject
- Olanzapine is a multi-acting receptor-targeted (atypical) antipsychotic administered to children for a variety of labelled and off-label indications.
- The pharmacokinetics (PK) of olanzapine have been previously characterized in adults and adolescents; however, the effects of growth and development on olanzapine PK, especially in children <10 years, remains unknown.

What this study adds
- This study characterizes developmental changes in olanzapine PK in a cohort of 45 subjects ranging in postnatal age from 2 months to 19 years.
- Body weight and postmenstrual age are influential covariates for characterizing developmental changes in olanzapine apparent clearance.
- We developed a paediatric dosing scheme that provided comparable plasma exposures to adults and adolescents. The proposed dosing scheme can be used to guide the development of prospective safety and efficacy studies for olanzapine in children.

2 METHODS

2.1 Patient population

PK samples used to develop the PopPK model were collected as part of the Pharmacokinetics of Understudied Drugs Administered to Children per Standard of Care (POPs) trial, a prospective, multi-centre, PK study in children less than 21 years of age (NICHDP-POP1-2011; ClinicalTrials.gov #NCT01431326) conducted by the Eunice Kennedy Shriver National Institute of Child Health and Human Development Pediatric Trials Network (PTN). Children who received olanzapine per standard of care as administered by their treating caregiver were eligible for enrolment. Exclusion criteria for the POPs trial included failure to obtain consent/assent or known pregnancy as determined by interview or testing. Additional exclusion criteria instituted for the current PK analysis included participants receiving dialysis (intermittent or continuous) or extracorporeal membrane oxygenation. The study protocol was reviewed and approved by each participating institution’s review board.

2.2 Drug dosing and sample collection

Dosing information was collected for up to eight doses prior to the sampling dose (last dose prior to sample collection). Since the POPs trial employs an opportunistic study design, the timing of plasma sample collections was dependent on standard of care laboratory assessments. However, parents/guardians were also given the option to allow sample collections at different times than standard of care laboratory tests. Results from standard of care laboratory tests (e.g., basic metabolic panel) were recorded if collected within 72 hours of the sampling dose. The PK analysis dataset was generated by The Emmes Company, LLC.
2.3 Analytical methods

Olanzapine concentrations in plasma were quantified using a validated liquid chromatography–tandem mass spectrometry (LC/MS–MS) assay (Frontage Laboratories, Exton, PA, USA). A Shimadzu series high-performance liquid chromatography system (Pump LC-20 AD; Autosampler SIL–20 AC HT) and a Sciex API 5000 system (mass spectrometer) were used for sample analysis. The separation was achieved using a Phenomenex Synergi MAX-RP 80 Å column (4 μm, 2 × 50 mm) at room temperature by gradient elution with 2mM ammonium hydroxide (95:5:0.05; mobile phase B). Intra- and inter-run accuracy and precision assessed at four concentration levels (0.05, 0.15, 6 and 37.5 ng/mL) were within the FDA bioanalytical assay validation criteria (e.g., ±15–20%). The lower limit of quantification for olanzapine was 0.05 ng/mL.

2.4 Population pharmacokinetic analysis

Olanzapine plasma concentration–time data were analysed using nonlinear mixed effects modelling using the software NONMEM (version 7.4, Icon Solutions, Ellicott City, MD, USA). The first-order conditional estimation method with interaction was used for all model runs. Run management was performed using Pirana (version 2.9.7). Non-parametric bootstraps were performed with Perl-speaks-NONMEM (version 3.6.2). Data manipulation and visualizations were performed in R (version 3.4.3, R Foundation for Statistical Computing, Vienna, Austria) and RStudio (version 1.1.383, RStudio, Boston, MA, USA) with the packages lattice, xpose4, cowplot, and ggplot2.

2.4.1 Base model development

One- and two-compartment structural models were explored. Inter-individual variability (IIV) on PK model parameters was described using an exponential relationship (Equation 1):

\[ P_J = \theta_{Pop} \times \exp(\eta_J) \]  

where \( P_J \) denotes the estimate of parameter \( J \) in the \( i \)th individual; \( \theta_{Pop} \) is the typical population value for parameter \( J \); and \( \eta_J \) denotes the deviation from the typical population value for parameter \( J \) in the \( i \)th individual. The random variable \( \eta \) is assumed to be normally distributed with a mean zero and variance \( \sigma^2 \). Estimation of diagonal and block matrices were explored to describe covariance between IIV terms. Proportional, additive and combined (proportional plus additive) residual error models were evaluated.

Based on standard practices, body size was empirically assumed to be an influential covariate for describing olanzapine PK. Correspondingly, competing body size measures, including body weight (WT), fat-free mass (FFM) and lean body mass (LBM), were assessed for model inclusion prior to evaluation of other covariates.

Equations used to estimate FFM and LBM are described in the supplementary materials. Fixed allometric relationships (i.e., exponent = 0.75) were employed to describe the relationship between clearance (CL) and inter-compartmental clearance (Q) with body size. For volume of distribution (V), a linear relationship was assumed (i.e., exponent = 1). Typical PK parameter values were centred towards a WT of 70 kg, LBM of 54 kg, or FFM of 56 kg.

2.4.2 Covariate testing

Forward selection and backward elimination were used to evaluate the influence of continuous and categorical covariates on olanzapine PK. The following continuous covariates were assessed: postnatal age (PNA; years), postmenstrual age (PMA; weeks), albumin (ALB; g/dL) and serum creatinine (SCR; mg/dL). In addition, the following categorical variable were assessed: sex (SEX); African American (RACE); obesity, defined as a body mass index ≥95th percentile for age and sex based on Centers for Disease Control and Prevention (CDC) growth charts; absence of food intake 2 hours prior to dose administration (FAST); formulation, tablet/capsule vs. crushed tablet/suspension/solution (FORM); and dose administration via tube (TUBE). Covariates were directly tested on all model parameters with added IIV terms. Statistical significance during covariate testing was asserted by comparing changes in objective function values (OFV) to critical values corresponding to chi-squared distributions with degrees of freedom equal to the difference in estimated parameters between nested models and \( P \)-values of .05 (forward selection) and .01 (backward elimination). Several imputation strategies were employed to account for missing covariates during the covariate testing process. For age (GA), which represents the sum of PNA and gestational age (GA), a GA of 40 weeks was assumed, if missing. For all children <120 days PNA. For children ≥120 days PNA, GA was reported, if available. An age-segmented approach was used to impute missing ALB and SCR values. Missing entries were imputed using the median value of covariate entries from participants within different age groups (PNA < 2 years, ≥2 and <6 years, ≥6 and <12 years and ≥12 years) for whom the covariate of interest was reported. Participants were assumed to be non-black/non-African American if the race was missing. Participants for whom obesity status was undefined (i.e., PNA < 2 years or missing body mass index) were assumed to be non-obese. Food intake prior to dose administration was only recorded for sampling doses. For non-sampling doses, fed-state conditions were assumed. All other covariates were non-missing within the dataset.

2.4.3 Model evaluation

Model development was guided by diagnostic plots, successful minimization and plausibility, as well as precision of parameter estimates, OFV and shrinkage values. Precision of parameter estimates from the final PopPK model were evaluated using non-parametric bootstrapping (1000 replicates) to generate 95% confidence intervals.
2.4.4 | Statistical analysis

Individual PK parameter estimates (e.g., Bayesian post-hoc) from the final PopPK model were computed and summarized for participants with PNA < 2 years, 2 to <6 years, 6 to <12 years, and ≥12 years. The Kruskal-Wallis test was performed to compare post-hoc clearance values (scaled to 70 kg) between age groups. A P-value of <.05 was used to assert statistical significance.

2.5 | Pharmacokinetically-guided dose optimizations

Optimal paediatric dosages were derived using a simulation-based methodology. Paediatric exposures (area under the plasma concentration–time curve; AUC) were computed for a virtual paediatric population of 4000 subjects (1000 subjects per PNA group: <2 years, 2–<6 years, 6–<12 years and ≥12 years). Virtual subjects were created using the PK-Sim® (v 7.2; https://github.com/Open-Systems-Pharmacology) population module. Subjects were created based on a White-American population with a male-to-female ratio of 50:50. The span of postnatal ages and body weights for virtual subjects were restricted to that of study participants who contributed data towards the PK analysis. All virtual subjects were considered full-term (GA = 40 weeks). This parameterization was based on a preliminary assessment of the PK dataset where only two of the seven subjects with GA reported were considered premature (e.g., <37 weeks gestational age). For each virtual subject, an individualized CL/F value was computed based on the final PopPK model, incorporating both fixed and random (e.g., IV) effects. Assuming linear pharmacokinetics, subject-specific plasma drug exposures (AUC) were derived using Equation 2.

\[
\text{AUC}_i = \frac{Dose_i}{CL/F_i}
\]  

where AUC<sub>i</sub> is the area under the plasma concentration–time curve for a participant (exposure; mg·h/L), Dose<sub>i</sub> is the dose administered to the participant (mg), and CL/F<sub>i</sub> is the participant-specific apparent clearance value (L/h). The computed AUC represents both single-dose exposure, from time 0 to infinity (AUC<sub>0-inf</sub>), and steady-state exposure, from 0 to the end of the dosing interval (AUC<sub>0-tau</sub>).

In the absence of a well-defined exposure–response relationship for olanzapine, a paediatric dosing scheme was derived to target comparable exposures to those achieved by adolescents and adults receiving oral doses of 2.5 and 5 mg. These doses reflect initial dose recommendations in adolescents for FDA labelled indications. In adults, 5 mg is the recommended initial dose of olanzapine when used in combination with fluoxetine for treating depressive episodes associated with bipolar I disorder and the lower limit of the recommended initial dosage for treatment of schizophrenia (i.e., 5–10 mg). Furthermore, dosages between 2.5 and 5 mg represent initial/target doses used in adults for several non-labelled indications. Different paediatric dosing schemes were explored to achieve comparable drug exposures to adults and adolescents. Average adult reference exposures were defined based on PK studies examining single-dose plasma exposure following oral administration of olanzapine in healthy non-smoking adult volunteers. Reported AUC (from 0 to infinity) values were averaged between publications, assuming linear PK between 2.5 and 10 mg doses, to provide reference exposures of 136.6 and 273.2 ng·h/mL for doses of 2.5 and 5 mg, respectively. To be defined as equivalent, median paediatric exposures derived by the proposed dosing scheme were required to fall within 80–125% of the adult reference value—a threshold that is widely used to assert bioequivalence (e.g., 80–125%). Instead of published studies directly reporting olanzapine exposures in adolescents, reference adolescent olanzapine exposures were estimated based on a previously published PopPK model by Lobo et al., who evaluated olanzapine PK in adolescents with schizophrenia or bipolar I patients. Briefly, CL/F values were simulated for a virtual population of 1000 adolescent subjects by incorporating both fixed and random-effect components. The population was generated using a similar demography as described above, except that the postnatal age and body weight ranges were constrained towards study participants included in Lobo et al.’s analysis (13–17 years and 41.1–148 kg, respectively). Adolescent exposures were estimated for fixed doses of 2.5 and 5 mg (Equation 2). Computed reference adolescent exposures were compared to adult reference exposures, as well as paediatric exposures estimated based on the proposed dosing scheme.

Lastly, a comparative dosing simulation was conducted to evaluate olanzapine exposures (i.e., AUC) achieved using standard of care dosing (based on the current study cohort) vs. the proposed paediatric dosing scheme. Dosing simulations were conducted for virtual subjects ≤6 years PNA using the developed PopPK model.

2.6 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in the IUPHAR/BPS Guide to PHARMACOLOGY, and are permanently archived in the Concise Guide to PHARMACOLOGY 2017/18.

3 | RESULTS

3.1 | Subject demographics

Eighty-eight plasma samples from 47 participants were included in the initial dataset. Five samples from two participants were excluded: one participant was receiving extracorporeal membrane oxygenation (one sample) and the other was the sole participant for whom PK samples were collected following intravenous dose administration (four samples). This participant was excluded owing to the paucity of data to characterize the intravenous disposition of olanzapine within the current analysis. The PK analysis dataset consisted of 83 plasma samples...
from 45 participants. All plasma samples were above the analytical lower limit of quantification. Demographic characteristics of participants included in the PK analysis are shown in Table 1. Eleven (24.4%) participants were obese. The median (range) number of doses recorded per participant was 8 (1–23). The median (range) average dose (per participant) was 0.1 (0.03–0.27) mg/kg. A median (range) of 2 (1–5) plasma samples were collected per participant. PK samples were collected under varying administration conditions (i.e., formulations, routes and feeding states), as specified in Table 2. Indications for olanzapine use were categorically recorded as schizophrenia, anxiety and ‘other’ for 1, 10 and 34 of the assessed participants, respectively. The dataset did not include information on concomitantly administrated drugs that could alter olanzapine disposition.

### 3.2 Pharmacokinetic analysis

A one-compartment model with first-order absorption, linear elimination and combined residual error provided an appropriate fit to the data. Empiric inclusion of alternative body size measures (FFM and LBM) as covariates on PK parameters did not result in improved model fits compared to actual body weight (WT); all models had similar OFV and goodness-of-fit plots (Supplementary Table S1 and Figure S1). Correspondingly, WT was selected as the preferred size scaler for development of the base model. Estimation of the first-order absorption rate constant (Ka) was associated with a high degree of imprecision and was subsequently fixed to 0.758 h⁻¹, a value previously defined for an adult PopPK model submitted to the FDA. The base model included IIV on CL/F solely. IIV terms on apparent volume

### Table 1 Clinical and demographic data (at time of first PK sample), summarized by age group

<table>
<thead>
<tr>
<th>Variable</th>
<th>Median (range or n (%))</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PNA &lt; 2 years</td>
</tr>
<tr>
<td>n</td>
<td>17</td>
</tr>
<tr>
<td>Postnatal age (years)</td>
<td>0.5 (0.2–1.7)</td>
</tr>
<tr>
<td>Gestational age (weeks)¹</td>
<td>38 (33–39.6)</td>
</tr>
<tr>
<td>Postmenstrual age (weeks)²</td>
<td>67.6 (46.7–126.4)</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>7.2 (4.2–11.5)</td>
</tr>
<tr>
<td>Body mass index (kg/m²)³</td>
<td>16.6 (12.8–19.6)</td>
</tr>
<tr>
<td>Albúmina (g/dL)⁴</td>
<td>2.9 (2.4–3.3)</td>
</tr>
<tr>
<td>Serum creatinine (mg/dL)⁵</td>
<td>0.4 (0.1–0.5)</td>
</tr>
<tr>
<td>Female</td>
<td>11 (64.7)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>Black or African American</td>
<td>2 (11.8)</td>
</tr>
<tr>
<td>Other</td>
<td>1 (5.9)</td>
</tr>
<tr>
<td>Unknown or not reported</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
</tr>
<tr>
<td>Hispanic or Latino</td>
<td>2 (11.8)</td>
</tr>
<tr>
<td>Not Hispanic or Latino</td>
<td>15 (88.2)</td>
</tr>
<tr>
<td>Ethnicity unknown or not reported</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Obese status⁶</td>
<td></td>
</tr>
<tr>
<td>Non-obese</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Obese</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Unavailable/not applicable</td>
<td>17 (100)</td>
</tr>
</tbody>
</table>

¹ Gestational age was reported for all children <120 days postnatal age (PNA). For children ≥120 days PNA, gestational age was reported, if available. Depicted values are representative of 7 subjects with postnatal ages of <2 years.
² Postmenstrual age computed as the sum of gestational and postnatal age. A gestational age of 40 weeks was imputed for subjects in whom gestational age was missing.
³ Body mass index was not reported for 2 subjects. Depicted values are representative of 16, 10, 10 and 7 subjects with PNA of <2 years, 2–<6 years, 6–<12 years, and ≥12 years, respectively.
⁴ Albúmina (serum) was not reported for 16 subjects. Depicted values are representative of 11, 7, 8 and 3 subjects with PNA of <2 years, 2–<6 years, 6–<12 years, and ≥12 years, respectively.
⁵ Serum creatinine was not reported for 2 subjects. Depicted values are representative of 17, 10, 11 and 5 subjects with PNA of <2 years, 2–<6 years, 6–<12 years, and ≥12 years, respectively.
⁶ Obesity defined as a body mass index ≥95th percentile for age and sex from Centers of Disease Control (CDC) growth charts⁴¹
of distribution (V/F) and $K_a$ were not estimated due to high shrinkage values.

Figure 1 displays random-effect terms for CL/F ($\text{ETA}_{\text{CL/F}}$) from the base model against selected covariates. CL/F values among younger participants were lower than typical model estimates (Figure 1A). Also, a slight trend towards higher clearance values among male participants was observed (Figure 1B). No discernible patterns associated with obesity status or race were denoted (Figures 1C, D). Following direct covariate testing (forward selection and backward elimination), only PMA met the threshold for model inclusion (Supplementary Table S2). This model, which included PMA (sigmoid $E_{\text{max}}$ submodel) and WT (fixed allometric exponent, 0.75), was subsequently denoted as the full model. As a final step, we compared the full model to an alternative model where the allometric exponent on WT was estimated rather than fixed. The alternative model resulted in a decrease in the OFV by 2.7 compared to the full model and produced similar goodness-of-fit plots (Supplementary Figure S2). However, the estimated typical CL/F, which is representative of a 70 kg subject at full maturation, differed between the two models: 21.6 vs. 16.8 L/h for the full and alternative models, respectively. A previously developed adolescent PopPK model for olanzapine reported typical CL/F estimates of 13.6 L/h (female adolescents) and 17.5 L/h (male adolescents); values that are comparable to the alternative model. Therefore, considering its external validity with respect to the published literature, the alternative model was defined as the final irreducible model. Model equations for the final model are described in Equations (3)–(5):

$$K_a \left( h^{-1} \right) = 0.758$$

$$CL/F_i \left( L \cdot h^{-1} \right) = 16.8 \times \left( \frac{WT_i}{70kg} \right)^{0.486} \times \frac{PMA_i^{3.977}}{70^{3.977} + PMA_i^{3.977}} \times \exp(\eta_{i,CL/F})$$

$\text{TABLE 2}$ Summary of PK samples

<table>
<thead>
<tr>
<th>Sample collection conditions</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feeding status</td>
<td></td>
</tr>
<tr>
<td>Fasted</td>
<td>32</td>
</tr>
<tr>
<td>Fed</td>
<td>51</td>
</tr>
<tr>
<td>Formulation</td>
<td></td>
</tr>
<tr>
<td>Suspension</td>
<td>14</td>
</tr>
<tr>
<td>Tablet</td>
<td>31</td>
</tr>
<tr>
<td>Crushed tablet</td>
<td>33</td>
</tr>
<tr>
<td>Capsule</td>
<td>5</td>
</tr>
<tr>
<td>Route</td>
<td></td>
</tr>
<tr>
<td>Oral</td>
<td>50</td>
</tr>
<tr>
<td>Nasogastric/orogastric tube</td>
<td>14</td>
</tr>
<tr>
<td>Transpyloric tube</td>
<td>10</td>
</tr>
<tr>
<td>Gastrostomy tube</td>
<td>7</td>
</tr>
<tr>
<td>Gastrostomy-jejunostomy tube</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>83</td>
</tr>
</tbody>
</table>

*aNo food intake 2 hours prior to drug administration.
*bExtemporaneous preparation.

FIGURE 1 Base PopPK model apparent clearance random-effect terms ($\text{ETA}_{\text{CL/F}}$) vs. selected covariates: (A) postmenstrual age; (B) sex; (C) obesity status; and (D) race. Dashed line represents a locally estimated scatterplot smoothing (LOESS) line.
where, $\eta_{\text{CL/F}}$ is the random-effect term associated with CL/F, WT is body weight (kg) and PMA is postmenstrual age in weeks for the $i$th subject. Estimated PopPK parameters and bootstrap approximations for the final model are listed in Table 3. Model parameter estimates based on the entire dataset were within 7% and 12% of median bootstrap approximations for fixed- and random-effect parameters, respectively. The bootstrap 95% confidence interval for the effect of WT on CL/F ($\theta_{\text{CL,WT}}$) spanned from −0.541 to 0.796. Imprecision of the bootstrap estimate was unsurprising considering the relatively small sample size and the need for bootstrap samples to contain participants with a diverse range of body sizes to provide an appropriate estimate of $\theta_{\text{CL,WT}}$ (i.e., its precision depends on a specific feature of the original sampling process). Comparatively, the estimate obtained from the entire dataset (including all participants) was determined with adequate precision (RSE = 36%). Goodness-of-fit plots for the final PopPK model demonstrated an appropriate fit with observed data (Figure 2).

When scaled to 70 kg, individualized apparent clearance estimates (CL/70kg/F) were statistically different between age groups (Kruskal-Wallis test; $P$-value < .05; Table 4). Post-hoc statistical testing indicated CL/70kg/F values were similar between younger age groups (2 to <6 years PNA and 6 to <12 years PNA) and adolescents (≥12 years PNA) except for infants (<2 years PNA), where values were significantly lower compared to adolescents (Kruskal-Wallis test; $P$-value < .05, Bonferroni-corrected). A parabolic relationship between olanzapine half-life and PNA was observed (Table 4 and Figure 3). Longer half-lives were observed in infants <5 months and children ≥6 years. For example, application of the proposed dosing strategy towards study participants would result in mean (range) olanzapine exposures in adolescents, derived based on Lobo et al.’s published PopPK model, were 24% higher compared to adult reference values. This observation was consistent with Lobo et al.’s investigation, where simulated olanzapine exposures were observed to be 27% higher in adolescents compared to adults. Dosages defined by the proposed dosing strategy were within a comparable range to standard of care dosages administered to subjects within the observed study cohort. For example, application of the proposed dosing strategy towards study participants would result in mean (range) olanzapine dosages of 0.054 (0.02–0.08) and 0.11 (0.04–0.16) mg/kg for strategies that target similar exposures to 2.5 and 5 mg doses in adults, respectively. Of note, both dosing strategies (Table 5) recommend

### Table 3: Final population PK model parameter estimates

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate</th>
<th>RSE (%)</th>
<th>2.5th percentile</th>
<th>Bootstrap median</th>
<th>97.5th percentile</th>
</tr>
</thead>
<tbody>
<tr>
<td>Structural model</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>KA (1/h)</td>
<td>0.758</td>
<td>FIX</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CL/F (L/h, 70 kg)</td>
<td>16.8</td>
<td>21</td>
<td>8.7</td>
<td>16</td>
<td>26.5</td>
</tr>
<tr>
<td>V/F (L, 70 kg)</td>
<td>663</td>
<td>13</td>
<td>523.3</td>
<td>677.3</td>
<td>914.1</td>
</tr>
<tr>
<td>TM50 (weeks)</td>
<td>70</td>
<td>16</td>
<td>52.5</td>
<td>69.8</td>
<td>317.3</td>
</tr>
<tr>
<td>HILL</td>
<td>3.97</td>
<td>23</td>
<td>2.08</td>
<td>4.15</td>
<td>7.08</td>
</tr>
<tr>
<td>$\theta_{\text{CL,WT}}$</td>
<td>0.486</td>
<td>36</td>
<td>−0.541</td>
<td>0.455</td>
<td>0.796</td>
</tr>
<tr>
<td>Random effects</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\omega_{\text{CL/F}}^2$ (CV%)</td>
<td>0.309 [60.2%]</td>
<td>38</td>
<td>0.035 [18.9%]</td>
<td>0.283 [57.2%]</td>
<td>0.688 [99.5%]</td>
</tr>
<tr>
<td>$\varepsilon^1$ - proportional error</td>
<td>0.0772</td>
<td>39</td>
<td>0.019</td>
<td>0.069</td>
<td>0.177</td>
</tr>
<tr>
<td>$\varepsilon^2$ - additive error</td>
<td>1.51</td>
<td>77</td>
<td>0.283</td>
<td>1.496</td>
<td>6.493</td>
</tr>
</tbody>
</table>

CL/F, clearance; CV, coefficient of variation; RSE, relative standard error; V/F, apparent volume of distribution; TM50, maturation half-life; HILL, hill coefficient; $\theta_{\text{CL,WT}}$, exponent modulating the influence of weight on apparent clearance.

Summary of 982 run of 1000 bootstrap runs that converged with ±3 significant digits.

$CV\% = 100 \times \sqrt[3]{\exp(\omega^2)} - 1$.}

3.3 | Optimal paediatric dosing simulations

The derived optimized paediatric dosing regimen used weight-normalized doses for children <6 months (PNA) or <15 kg and fixed doses for children ≥15 kg (Table 5). Since the PK of olanzapine was described using a linear PK model, the proposed dosing regimen and simulation-based graphical plots for the 5 mg dose (Supplementary Figure S3) represent a superposition of the 2.5 mg dose (Figure 4). Median AUC values across the different paediatric dosing groups fell within 80–125% of the adult reference value (Figure 4A). A similar finding was also observed when median exposures were summarized across the age range of 0.2–19 years (Figure 4B). Median reference exposures in adolescents, derived based on Lobo et al.’s published PopPK model, were 24% higher compared to adult reference values. Median exposures for the 966 virtual paediatric subjects from the ≥50 kg dosing group, which comprised exclusively adolescent subjects (i.e., ≥12 years), was comparable to reference adolescent values derived from Lobo et al.’s model. For example, after administration of 2.5 mg, median plasma exposures were 153.6 and 170.1 ng·h/mL for the ≥50 kg dosing group and the adolescent reference group, respectively. This result demonstrates the external agreement between simulated exposures generated from our model and Lobo et al.’s adolescent PopPK model. Dosages defined by the proposed dosing strategy (Table 5) were within a comparable range to standard of care dosages administered to subjects within the observed study cohort. For example, application of the proposed dosing strategy towards study participants would result in mean (range) olanzapine dosages of 0.054 (0.02–0.08) and 0.11 (0.04–0.16) mg/kg for strategies that target similar exposures to 2.5 and 5 mg doses in adults, respectively. Of note, both dosing strategies (Table 5) recommend
lower olanzapine dosages for subjects ≤6 months postnatal age than were administered per standard of care (Supplementary Figure S4). Correspondingly, model simulations depicted higher AUC values for children ≤6 months receiving the median standard of care dosage from this study (≤0.1 mg/kg) compared to estimates derived from the proposed dosing strategy (Supplementary Figure S5).

### DISCUSSION

Using opportunistically-collected PK samples, our investigation characterized the PopPK of enterally-administered olanzapine in children ranging from 2 months to 19 years (PNA). To our knowledge, this is the first report of the PK of olanzapine in children <10 years. Similar to other published PopPK models for olanzapine in adolescents and

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**TABLE 4** Individual empiric Bayesian post-hoc parameter estimates from the final population PK model

<table>
<thead>
<tr>
<th>PNA (years)</th>
<th>n</th>
<th>CL/F (L/h/kg)</th>
<th>CL$_{70kg}$/F (L/h)</th>
<th>Half-life (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;2 years</td>
<td>17</td>
<td>0.35 (0.14–1.41)</td>
<td>7.86 (2.32–31.39)</td>
<td>18.56 (4.65–46.65)</td>
</tr>
<tr>
<td>2–&lt;6 years</td>
<td>10</td>
<td>0.50 (0.18–1.7)</td>
<td>15.16 (7.23–50.31)</td>
<td>13.36 (3.86–35.86)</td>
</tr>
<tr>
<td>6–&lt;12 years</td>
<td>11</td>
<td>0.24 (0.15–0.78)</td>
<td>13.96 (6.34–44.71)</td>
<td>26.92 (8.42–42.72)</td>
</tr>
<tr>
<td>≥12 years</td>
<td>7</td>
<td>0.23 (0.12–0.47)</td>
<td>18.69 (8.74–34.01)</td>
<td>28.93 (14.11–56.44)</td>
</tr>
<tr>
<td>Overall</td>
<td>45</td>
<td>0.37 (0.12–1.7)</td>
<td>12.79 (2.32–50.31)</td>
<td>17.65 (3.86–56.44)</td>
</tr>
</tbody>
</table>

aData are expressed as median (min-max).
PNA, postnatal age; CL/F, olanzapine apparent clearance; CL$_{70kg}$/F, olanzapine apparent clearance scaled to 70 kg.
adults, we found a one-compartment structural model was sufficient to characterize the PK of olanzapine. Furthermore, the estimated typical apparent clearance for a 70 kg adult derived from our model (16.8 L/h) was comparable to previous PK analyses in adult non-smoking healthy volunteers, Alzheimer’s disease patients and schizophrenia patients that report mean clearance values between 16.1 and 20 L/h. In contrast, our model overpredicted apparent clearance values compared to a PK analysis by Grothe et al., who examined olanzapine disposition in eight children aged 10–18 years with treatment-resistant schizophrenia. For these subjects, the median (range) typical apparent clearance estimate from our model was 15.5 (14.1–21.1) L/h; whereas, the study estimated value, determined by non-compartmental analysis, was 9.35 (5.8–14.3) L/h. The aetiology for this discrepancy is not entirely clear as our study also included participants of a similar age. Of note, however, typical apparent clearance estimates generated by a competing olanzapine PopPK model developed in adolescents also overpredicted clearance values compared to Grothe et al.’s study. For example, the median (range) typical apparent clearance estimate for the eight children based on Lobo et al.’s model was 15.3 (12–22.3) L/h.

The use of theoretical (i.e., fixed to 0.75) vs. estimated allometric exponents for predicting drug clearance in children is a heavily debated topic in current literature. Despite the limited size of our analysis dataset (45 participants; 83 samples) and the finding that both theoretical and estimated exponent models provided similar fits to the data (Supplementary Figure S2), we opted to use an estimated exponent (i.e., 0.486) to describe the relationship between weight and olanzapine clearance for two reasons. First, use of an estimated exponent provided a typical clearance estimate (scaled to a 70 kg subject) that was in better agreement with values from two published PopPK models for olanzapine in adults and adolescents that were developed using datasets comprising >100 subjects each. Second, our dataset included participants with consistent representation along the developmental trajectory (from infants to adolescents) and a diverse range of body sizes (from 4.2 to 111.7 kg) that permitted for estimation of the allometric exponent with a moderate degree of precision (36% RSE).
Individualized PK estimates (i.e., Bayesian post hoc) indicated the presence of a parabolic relationship between olanzapine half-life and age (Figure 3). This pattern can be attributed to the ontogeny of physiological processes modulating olanzapine hepatic clearance, which have yet to reach full maturation in younger children. A similar trend is observed for sufentanil, a heptically metabolized synthetic opioid, which exhibits a shorter terminal half-life among infants and children compared to neonates and adults.\(^54,55\)

For olanzapine, current FDA labelling only includes indications for children ≥10 years, indicating that olanzapine is exclusively administered off-label to children <10 years.\(^12\) A high prevalence of off-label use was observed in the current study cohort with only one participant receiving olanzapine for a regulatory-approved indication, schizophrenia. For 10 participants, the indication for olanzapine therapy was denoted as anxiety, while for the remaining 34 participants, the indication was denoted as “other.” Among these subjects, the reported indication of olanzapine use was agitation, delirium, nausea, sedation or weening of sedative medications, and unclear/not recorded for 13, 10, 5, 3 and 3 participants, respectively. Considering that even when administered for labelled indications in adults, studies offer inconsistent evidence to support a relationship between olanzapine PK (e.g., plasma concentrations) and efficacy, development of a paediatric dosing scheme targeting specific PK thresholds associated with efficacy was implausible.\(^19-23\) Consequently, we chose to identify paediatric doses that would achieve comparable exposures (AUC) to adults and adolescents receiving regulatory-labelled initial doses. When taking into account the lack of paediatric safety and efficacy studies for olanzapine, especially in children <10 years, using such a dosing scheme cannot be fully supported. Drug safety profiles established in adults cannot be universally extrapolated to children; studies examining adverse drug events associated with olanzapine have demonstrated divergent patterns between adults and children.\(^9,56\) For example, incidences of weight gain and sedation were >10% higher in children (>10 years of age) compared to adults (absolute risk difference).\(^9\) Correspondingly, a rational use of the proposed dosing scheme would be to inform the development of pivotal safety and efficacy studies in children.

For children ≥7 months PNA and ≥15 kg, the proposed dosing scheme recommends fixed doses based on either full tablets (2.5 or 5 mg) or fractions of tablets (½ or ¾). Nevertheless, to maintain exposure targets in children ≤6 months (PNA) or ≤15 kg, weight-normalized (mg/kg) dosing would be required. Accurate administration of such dosages requires a flexible formulation such as suspension or solution. Although such a formulation is unavailable commercially, information on extemporaneous preparation of an olanzapine suspension is available in the literature.\(^57,58\)

Several limitations were associated with the current PK analysis. First, owing to the relatively small size and sparse nature of the analysed dataset (45 participants; 83 samples), the power of our analysis to identify influential covariates was limited. Previous PopPK studies in adults and adolescents with larger sample sizes (>100 participants) have identified race (African American) and/or sex as influential covariates affecting olanzapine apparent clearance.\(^25,29,30\) Although both these covariates were tested in our analysis, neither met the criteria for model inclusion. Similarly, the power of our analysis to detect influential covariates related to different administration routes and formulations was limited. Second, our dosing simulations were based on a racially homogeneous population (i.e., White-American population), representative of the demographics of the majority (~84.4%) of study participants. As our final model did not include race as an influential covariate towards olanzapine PK, the generated population only contributed information pertaining to subject weight and age. Since the proposed dosing strategy utilized weight-based classifications for the majority of subjects (i.e., ≥7 months postnatal age), the use of different virtual populations was not anticipated to exert a substantial effect on the results of the analysis. However, as PopPK models are empiric in nature, caution should be exercised if applying such models to simulate populations outside their scope of development. Third, the dataset did not contain information pertaining to potentially influential covariates such as interacting medications and smoking status. For example, co-administration of fluvoxamine in adults has been shown to decrease olanzapine apparent clearance by 42%.\(^59\) Additionally, in adult smokers, olanzapine apparent clearance was observed to be 55% higher relative to non-smokers.\(^29\) For our analysis, exclusion of smoking status as a covariate was not inferred to be of substantial impact considering the age range of study participants (i.e., prevalence of smoking anticipated to be minor). Lastly, the dosing strategy developed from this work is based on PK considerations only. Since paediatric use of olanzapine is frequently for off-label indications, where relationships between dose/systemic concentrations and efficacy need to be substantiated, prospective safety and efficacy studies for paediatric indications of interest are needed to fully support using such a dosing strategy.

5 | CONCLUSION

Using opportunistically-collected PK samples, we developed a PopPK model for enterally-administered olanzapine in subjects ranging from 2 months to 19 years. Our analysis identified PMA and body weight as influential covariates for describing developmental changes in olanzapine apparent clearance. Simulations from the final model were used to develop an age- and weight-based dosing scheme for children that provided comparable exposures to adults and adolescents. This dosing scheme can serve as a guide for the development of prospective safety and efficacy studies to promote the judicious use of olanzapine in children.

THE EUNICE KENNEDY SHRIVER NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT (NICHD)
Perdita Taylor-Zapata and June Lee.

THE EMMES COMPANY, LLC CORPORATION (DATA COORDINATING CENTER)
Ravinder Anand, Gaurav Sharma, Gina Simone, Kim Kaneshige, and Lawrence Taylor.
PTN PUBLICATION COMMITTEE
Chaired by Thomas Green, Ann & Robert H. Lurie Children’s Hospital of Chicago, Chicago, IL.

Pediatric Trials Network’s Pharmacokinetics of Understudied Drugs Administered to Children per Standard of Care Study Team and Study Coordinators
Duke Clinical Research Institute: Chiara Melloni (PI), Barrie Harper (PL), Adam Samson (L-CRA), Tammy Day (CRA).
Hospital Sainte-Justine: Julie Autmizguine (PI), Mariana Dumitrascu (SC).
Ann and Robert H. Lurie Children’s Hospital of Chicago: Rami Yoge (PI), Laura Fearn (SC).
Oregon Health and Science University: Amira Al-Uzri (PI), Kira Clark (SC).
University of Utah Hospitals and Clinics: Catherine Sherwin (PI), Sharada Dixit (SC).
Cincinnati Children Hospital Medical Center: Stuart Goldstein (PI), Teresa Mottes (SC), Tara Terrell (SC).
Duke University Medical Center: Kevin Watt (PI), Samantha Wrenn (SC), Christie Milleson (SC), Melissa Harward (SC).
The Children’s Hospital Research Institute of Manitoba, Inc.: Geert T’Jong (PI), Jeanninne Schellenberg (SC).
The Hospital for Sick Children: Yaron Finkelstein (PI), Maggie Rumanitri (SC).
University of Florida Center for HIV/AIDS Research Education and Service (UF CARES): Mobeen H. Rathore, MD (PI), Kathleen Thoma (SC).

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CONTRIBUTORS
C.P.H. came up with the concept for the study, and designed the study together with A.R.M. All the authors were responsible for the acquisition, analysis, or interpretation of the data. C.P.H. and A.R.M. drafted the manuscript. All authors were responsible for critical revision of the manuscript for important intellectual content.

DATA AVAILABILITY STATEMENT
To help expand the knowledge base for paediatric medicine, the Pediatric Trials Network is pleased to share data from its completed and published studies with interested investigators. For requests, please contact: ptn-program-manager@dm.duke.edu.

ORCID
Catherine M.T. Sherwin https://orcid.org/0000-0002-0844-3207
Kevin Watt https://orcid.org/0000-0002-5975-5091
Christoph P. Hornik https://orcid.org/0000-0001-7056-8759

REFERENCES


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