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ORIGINAL ARTICLE

Population pharmacokinetics of olanzapine in children

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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

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indications (i.e., off-label).[5] 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.[6–8] 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.[9] Consequently, to promote the safe and effective use of antipsychotic medications 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 ($5\text{-HT}_{2A/2B/2C}$), dopamine (D_2), histamine (H_1) and adrenergic receptors (α_1).[10,11] 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.[12] 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.[13–18] Despite olanzapine's diverse usage, the relationship between specific PK thresholds (e.g., pre-dose plasma concentrations) and therapeutic efficacy remains ill-defined.[19–23] Furthermore, few studies exist characterizing the PK of olanzapine in children, especially those <10 years.[24,25]

In adults, the oral bioavailability of olanzapine is reported to be ≥65%.[26] On average, plasma protein binding is 93% and attributed to both albumin and α-1-acid glycoprotein.[12,26] Olanzapine is primarily cleared by hepatic metabolism via several enzymes (CYP1A2, CYP2D6, CYP2C8, UGT1A4, and flavin-containing monooxygenase-3), while ~7% of the orally administered dose is excreted unchanged in urine.[26–28] Previous adult PK investigations indicate that smoking status, sex and race (African American) are significant covariates towards olanzapine apparent oral clearance (CL/F).[29,30] In adolescents, body weight and sex have been identified as influential covariates.[25] 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.

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 (NICHD-POP01–2011; 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

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.

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 acetate in water (mobile phase A) and acetonitrile:water: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%).[31] 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).[32] Nonparametric bootstraps were performed with Perl-speaks-NONMEM (version 3.6.2).[33] 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.[34–37]

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):

$$P_{ij} = \theta_{Pop,j} * \exp(\eta_{ij}) \tag{1}$$

where P_{ij} denotes the estimate of parameter j in the ith individual; $\theta_{Pop,j}$ is the typical population value for parameter j; and η_{ij} denotes the deviation from the typical population value for parameter j in the ith individual. The random variable η is assumed to be normally distributed with a mean zero and variance ω^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.[38] 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.[39,40] 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[41] (OBESE); 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 PMA, which represents the sum of PNA and gestational age (GA), a GA of 40 weeks was assumed, if missing. GA age was reported 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., IIV) effects. Assuming linear pharmacokinetics, subject-specific plasma drug exposures (AUC) were derived using Equation 2.

$$AUC_i = \frac{Dose_i}{CL/F_i} \qquad (2)$$

where AUC_i is the area under the plasma concentration–time curve for a participant (exposure; mg*h/L), $Dose_i$ is the dose administered to the participant (mg), and CL/F_i is the participant-specific apparent clearance value (L/h). The computed AUC represents both single-dose exposure, from time 0 to infinity (AUC_{0-inf}), and steady-state exposure, from 0 to the end of the dosing interval (AUC_{0-tau}).

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.[12] 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).[12] Furthermore, dosages between 2.5 and 5 mg represent initial/target doses used in adults for several non-labelled indications.[42–45] 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.[46–48] 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%).[49] 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.,[25] 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 http://www.guidetopharmacology.org, the common portal for data from 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 model 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 (K_a) 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.[50] 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

Variable	Median (range) or n (%)				
	PNA < 2 years	PNA 2–< 6 years	PNA 6–< 12 years	PNA ≥ 12 years	All
n	17	10	11	7	45
Postnatal age (years)	0.5 (0.2–1.7)	3.4 (2.2–5.2)	9.2 (6.2–11.3)	16.6 (12.7–19.2)	3.8 (0.2–19.2)
Gestational age (weeks)[a]	38 (33–39.6)	-	-	-	38 (33–39.6)
Postmenstrual age (weeks)[b]	67.6 (46.7–126.4)	216.3 (156–312.6)	522.9 (365.3–632)	904.7 (702.1–1043.9)	239.7 (46.7–1043.9)
Body weight (kg)	7.2 (4.2–11.5)	14.1 (10.9–23)	29.1 (15.8–74.8)	80.2 (61–111.7)	14.1 (4.2–111.7)
Body mass index (kg/m^2)[c]	16.6 (12.8–19.6)	16.9 (12.9–21.9)	17.2 (14.8–31.9)	32.1 (23.2–40.1)	18 (12.8–40.1)
Albumin (g/dL)[d]	2.9 (2.4–3.3)	2.6 (2–3.3)	3.2 (2.1–4.3)	2.9 (1.5–3.9)	2.9 (1.5–4.3)
Serum creatinine (mg/dL)[e]	0.4 (0.1–0.5)	0.2 (0.1–0.4)	0.3 (0.2–0.6)	0.7 (0.5–1)	0.4 (0.1–1)
Female	11 (64.7)	4 (40)	5 (45.5)	4 (57.1)	24 (53.3)
Race					
White	14 (82.4)	9 (90)	9 (81.8)	6 (85.7)	38 (84.4)
Black or African American	2 (11.8)	1 (10)	1 (9.1)	0 (0)	4 (8.9)
Other	1 (5.9)	0 (0)	0 (0)	1 (14.3)	2 (4.4)
Unknown or not reported	0 (0)	0 (0)	1 (9.1)	0 (0)	1 (2.2)
Ethnicity					
Hispanic or Latino	2 (11.8)	0 (0)	5 (45.5)	1 (14.3)	8 (17.8)
Not Hispanic or Latino	15 (88.2)	10 (100)	6 (54.5)	5 (71.4)	36 (80)
Ethnicity unknown or not reported	0 (0)	0 (0)	0 (0)	1 (14.3)	1 (2.2)
Obese status[f]					
Non-obese	0 (0)	7 (70)	8 (72.7)	1 (14.3)	16 (35.6)
Obese	0 (0)	3 (30)	2 (18.2)	6 (85.7)	11 (24.4)
Unavailable/not applicable	17 (100)	0 (0)	1 (9.1)	0 (0)	18 (40)

[a]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.

[b]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.

[c]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.

[d]Albumin (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.

[e]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.

[f]Obesity defined as a body mass index ≥95th percentile for age and sex from Centers of Disease Control (CDC) growth charts.[41]

TABLE 2 Summary of PK samples

Sample collection conditions	n
Feeding status	
Fasted[a]	32
Fed	51
Formulation	
Suspension[b]	14
Tablet	31
Crushed tablet	33
Capsule	5
Route	
Oral	50
Nasogastric/orogastric tube	14
Transpyloric tube	10
Gastrostomy tube	7
Gastrostomy-jejunostomy tube	2
Total	83

[a]No food intake 2 hours prior to drug administration.
[b]Extemporaneous preparation.

of distribution (V/F) and K_a were not estimated due to high shrinkage values.

Figure 1 displays random-effect terms for CL/F (ETA$_{CL/F}$) 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$_{max}$ 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.[25] 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):

$$K_a\left(h^{-1}\right) = 0.758 \tag{3}$$

$$CL/F_i\left(L \cdot h^{-1}\right) = 16.8 * \left(\frac{WT_i}{70\,kg}\right)^{0.486} * \frac{PMA_i^{3.97}}{70^{3.97} + PMA_i^{3.97}} * \exp\left(\eta_{i,CL/F}\right) \tag{4}$$
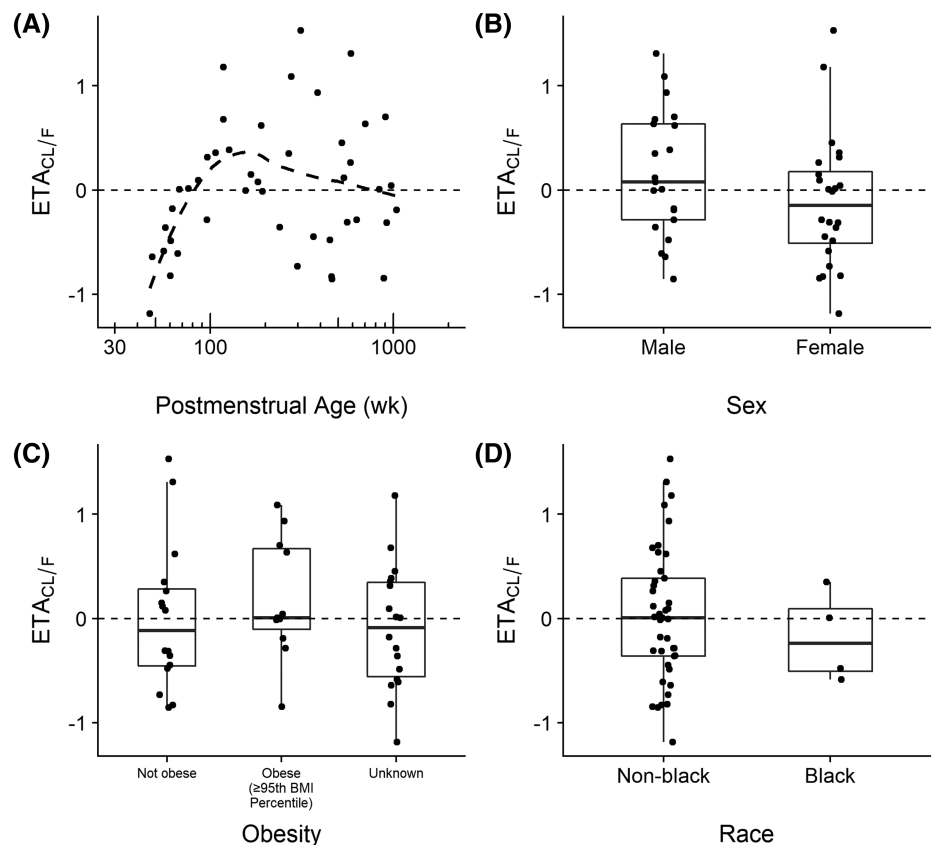

FIGURE 1 Base PopPK model apparent clearance random-effect terms (ETA$_{CL/F}$) *vs.* selected covariates: (A) postmenstrual age; (B) sex; (C) obesity status; and (D) race. Dashed line represents a locally estimated scatterplot smoothing (LOESS) line

$$V/F_i (L) = 663 * \left(\frac{WT_i}{70\,kg}\right)^1 \qquad (5)$$

where, $\eta_{i,CL/F}$ is the random-effect term associated with CL/F, WT_i is body weight (kg) and PMA_i is postmenstrual age in weeks for the ith 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 ($\theta_{CL,WT}$) 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 $\theta_{CL,WT}$ (i.e., its precision depends on a specific feature of the original sampling process).[51] 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. Comparatively, shorter half-lives were observed for participants aged 6 months to <6 years.

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. 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.[25]

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.[25] 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.[25] 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

TABLE 3 Final population PK model parameter estimates

Parameter	Estimate	RSE[a] (%)	2.5th percentile	Bootstrap median	97.5th percentile
Structural model					
KA (1/h)	0.758	FIX			
CL/F (L/h, 70 kg)	16.8	21	8.7	16	26.5
V/F (L, 70 kg)	663	13	523.3	677.3	914.1
TM_{50} (weeks)	70	16	52.5	69.8	317.3
HILL	3.97	23	2.08	4.15	7.08
$\theta_{CL,WT}$	0.486	36	−0.541	0.455	0.796
Random effects					
$\omega_{CL/F}^2$ (CV% [b])	0.309 [60.2%]	38	0.035 [18.9%]	0.283 [57.2%]	0.688 [99.5%]
ε_1^2 – proportional error	0.0772	39	0.019	0.069	0.177
ε_2^2 – additive error	1.51	77	0.283	1.496	6.493

CL/F, clearance; CV, coefficient of variation; RSE, relative standard error; V/F, apparent volume of distribution; TM_{50}, maturation half-life; HILL, hill coefficient; $\theta_{CL,WT}$, exponent modulating the influence of weight on apparent clearance.
[a]Summary of 982 run of 1000 bootstrap runs that converged with ≥3 significant digits.
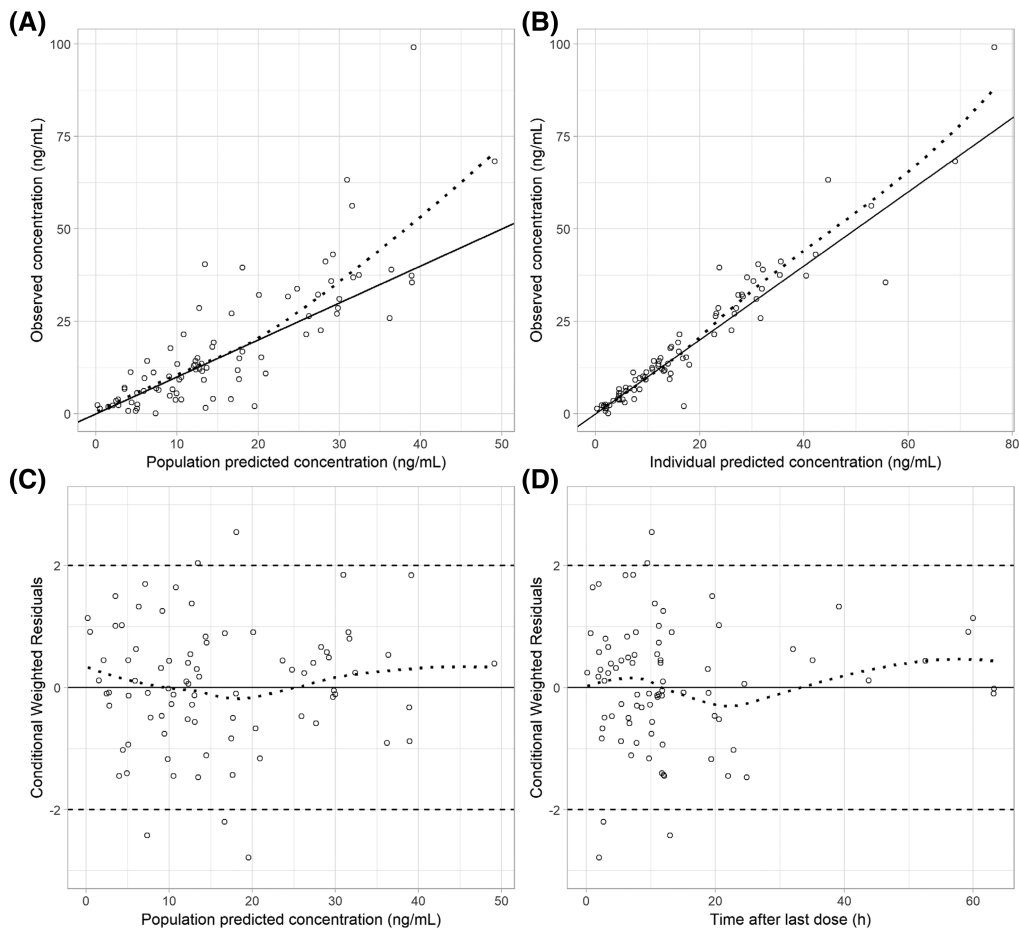[b]$CV\% = 100 * \sqrt{\exp(\omega^2) - 1}$.

FIGURE 2 Goodness-of-fit plots for the final PopPK model: (A) observed *vs.* population predicted concentrations; (B) observed *vs.* individual predicted concentrations; (C) conditional weighted residuals *vs.* population predicted concentrations; and (D) conditional weighted residuals *vs.* time after last dose. In (A) and (B), the line of identity is depicted by the solid line. In all subplots, dotted lines depict locally estimated scatterplot smoothing (LOESS) lines

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

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

[a]Data are expressed as median (min-max).
PNA, postnatal age; CL/F, olanzapine apparent clearance; CL$_{70kg}$/F, olanzapine apparent clearance scaled to 70 kg

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).

4 | 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
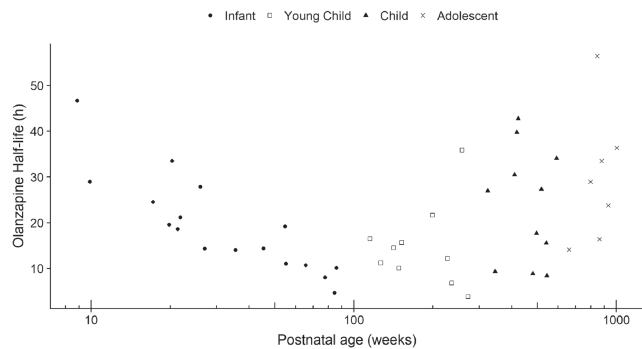
Postnatal ages of observed subjects: infants (0.2-1.7 years); young child (2.5-5.2 years); child (6.2-11.3 years); and adolescent (12.7-19.2 years).

FIGURE 3 Individualized half-life estimates *vs.* postnatal age based on the final PopPK model

TABLE 5 Optimized paediatric dosing to achieve comparable plasma exposures to adults

Group	2.5 mg[a]	5 mg[b]
2–6 months (postnatal age)	0.0375 mg/kg	0.075 mg/kg
<15 kg[c]	0.075 mg/kg	0.15 mg/kg
15–29 kg[c]	1.25 mg	2.5 mg
30–50 kg[c]	1.875 mg	3.75 mg
≥50 kg[c]	2.5 mg	5 mg

[a]Paediatric dosages to target an area under the plasma concentration–time curve comparable to healthy adult volunteers receiving a 2.5 mg oral dose.
[b]Paediatric dosages to target an area under the plasma concentration–time curve comparable to healthy adults volunteers receiving a 5 mg oral dose.
[c]Dosing applicable to subjects ≥7 months, postnatal age.

adults, we found a one-compartment structural model was sufficient to characterize the PK of olanzapine.[25,29] 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.[29,46–48] 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.[24] 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.[24] 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.[25] 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.[25]

The use of theoretical (i.e., fixed to 0.75) *vs.* estimated allometric exponents for predicting drug clearance in children is a heavily
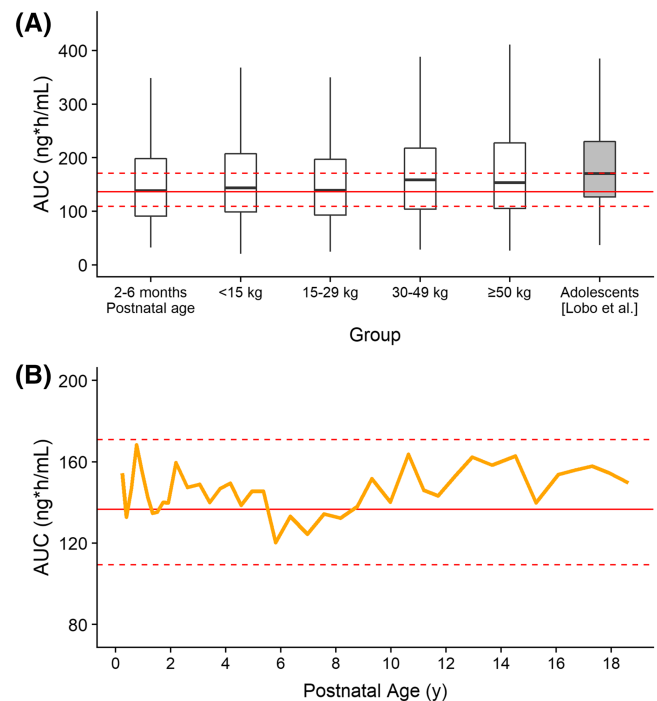

FIGURE 4 Area under the plasma concentration–time curve (AUC_{0-inf}) simulations based on the proposed paediatric dosing scheme (Table 5) that targets olanzapine exposures similar to adults and adolescents receiving 2.5 mg (oral). Simulated AUC_{0-inf} values were computed for a virtual population consisting of 4000 virtual subjects with ages and weights truncated towards the demographics of the current study (i.e., 0.17–19 years postnatal age; 4–111 kg body weight) using the developed paediatric PopPK model. In subplot A, AUC_{0-inf} values are summarized between different paediatric dosing groups (no fill). Reference adolescent exposures simulated based on a previously developed adolescent PopPK model (Lobo et al.[25]) were computed using a virtual population of 1000 adolescent subjects and an oral dose of 2.5 mg (grey fill). In subplot B, the running 50th percentile (median) of simulated AUC_{0-inf} values generated from the developed paediatric PopPK model are displayed by age (4000 virtual subjects; solid yellow line). The average AUC_{0-inf} for non-smoking adults (red solid line) along with 80% and 125% thresholds for this value (red dashed lines) are display for reference [46–48]

debated topic in current literature.[38,52,53] 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.[25,29] 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 hepatically 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.

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.

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REFERENCES

1. Hales CM, Kit BK, Gu Q, Ogden CL. Trends in prescription medication use among children and adolescents—United States, 1999-2014. *JAMA*. 2018;319(19):2009-2020.
2. Olfson M, Blanco C, Liu SM, Wang S, Correll CU. National trends in the office-based treatment of children, adolescents, and adults with antipsychotics. *Arch Gen Psychiatry*. 2012;69(12):1247-1256.
3. Zito JM, Burcu M, Ibe A, Safer DJ, Magder LS. Antipsychotic use by Medicaid-insured youths: impact of eligibility and psychiatric diagnosis across a decade. *Psychiatr Serv*. 2013;64(3):223-229.
4. Arora N, Knowles S, Gomes T, et al. Interprovincial variation in antipsychotic and antidepressant prescriptions dispensed in the Canadian pediatric population. *Can J Psychiatry*. 2016;61(12):758-765.
5. Sohn M, Moga DC, Blumenschein K, Talbert J. National trends in off-label use of atypical antipsychotics in children and adolescents in the United States. *Medicine (Baltimore)*. 2016;95(23):e3784.
6. Bellis JR, Kirkham JJ, Nunn AJ, Pirmohamed M. Adverse drug reactions and off-label and unlicensed medicines in children: a prospective cohort study of unplanned admissions to a paediatric hospital. *Br J Clin Pharmacol*. 2014;77(3):545-553.
7. Horen B, Montastruc JL, Lapeyre-Mestre M. Adverse drug reactions and off-label drug use in paediatric outpatients. *Br J Clin Pharmacol*. 2002;54(6):665-670.

8. Laughon MM, Benjamin DK Jr, Capparelli EV, et al. Innovative clinical trial design for pediatric therapeutics. *Expert Rev Clin Pharmacol*. 2011;4(5):643-652.

9. Liu XI, Schuette P, Burckart GJ, et al. A comparison of pediatric and adult safety studies for antipsychotic and antidepressant drugs submitted to the United States Food and Drug Administration. *J Pediatr*. 2019;208:236-242.

10. Bymaster FP, Nelson DL, DeLapp NW, et al. Antagonism by olanzapine of dopamine D1, serotonin2, muscarinic, histamine H1 and alpha 1-adrenergic receptors in vitro. *Schizophr Res*. 1999;37(1):107-122.

11. Mauri MC, Paletta S, Maffini M, et al. Clinical pharmacology of atypical antipsychotics: an update. *EXCLI J*. 2014;13:1163-1191.

12. National Library of Medicine (US). Label: Olanzapine—olanzapine tablet in DailyMed. DailyMed web site. https://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=d974d2a4-fc65-42ff-8138-cfcfd7381534. Updated 15 October 2018. Accessed 23 January 2020.

13. Dennis K, Le Grange D, Bremer J. Olanzapine use in adolescent anorexia nervosa. *Eat Weight Disord*. 2006;11(2):e53-e56.

14. Holzer B, Lopes V, Lehman R. Combination use of atomoxetine hydrochloride and olanzapine in the treatment of attention-deficit/-hyperactivity disorder with comorbid disruptive behavior disorder in children and adolescents 10-18 years of age. *J Child Adolesc Psychopharmacol*. 2013;23(6):415-418.

15. Kemner C, Willemsen-Swinkels SH, de Jonge M, Tuynman-Qua H, van Engeland H. Open-label study of olanzapine in children with pervasive developmental disorder. *J Clin Psychopharmacol*. 2002;22(5):455-460.

16. Malone RP, Cater J, Sheikh RM, Choudhury MS, Delaney MA. Olanzapine versus haloperidol in children with autistic disorder: an open pilot study. *J Am Acad Child Adolesc Psychiatry*. 2001;40(8):887-894.

17. Stephens RJ, Bassel C, Sandor P. Olanzapine in the treatment of aggression and tics in children with Tourette's syndrome—a pilot study. *J Child Adolesc Psychopharmacol*. 2004;14(2):255-266.

18. Sassano-Higgins S, Freudenberg N, Jacobson J, Turkel S. Olanzapine reduces delirium symptoms in the critically ill pediatric patient. *J Pediatr Intensive Care*. 2013;2(2):49-54.

19. Bergemann N, Frick A, Parzer P, Kopitz J. Olanzapine plasma concentration, average daily dose, and interaction with co-medication in schizophrenic patients. *Pharmacopsychiatry*. 2004;37(2):63-68.

20. Bishara D, Olofinjana O, Sparshatt A, Kapur S, Taylor D, Patel MX. Olanzapine: a systematic review and meta-regression of the relationships between dose, plasma concentration, receptor occupancy, and response. *J Clin Psychopharmacol*. 2013;33(3):329-335.

21. Citrome L, Stauffer VL, Chen L, et al. Olanzapine plasma concentrations after treatment with 10, 20, and 40 mg/d in patients with schizophrenia: an analysis of correlations with efficacy, weight gain, and prolactin concentration. *J Clin Psychopharmacol*. 2009;29(3):278-283.

22. Fellows L, Ahmad F, Castle DJ, Dusci LJ, Bulsara MK, Ilett KF. Investigation of target plasma concentration–effect relationships for olanzapine in schizophrenia. *Ther Drug Monit*. 2003;25(6):682-689.

23. Lu ML, Chen CH, Kuo PT, Lin CH, Wu TH. Application of plasma levels of olanzapine and N-desmethyl-olanzapine to monitor metabolic parameters in patients with schizophrenia. *Schizophr Res*. 2018;193:139-145.

24. Grothe DR, Calis KA, Jacobsen L, et al. Olanzapine pharmacokinetics in pediatric and adolescent inpatients with childhood-onset schizophrenia. *J Clin Psychopharmacol*. 2000;20(2):220-225.

25. Lobo ED, Robertson-Plouch C, Quinlan T, Hong Q, Bergstrom RF. Oral olanzapine disposition in adolescents with schizophrenia or bipolar I disorder: a population pharmacokinetic model. *Paediatr Drugs*. 2010;12(3):201-211.

26. Kassahun K, Mattiuz E, Nyhart E Jr, et al. Disposition and biotransformation of the antipsychotic agent olanzapine in humans. *Drug Metab Dispos*. 1997;25(1):81-93.

27. Callaghan JT, Bergstrom RF, Ptak LR, Beasley CM. Olanzapine. Pharmacokinetic and pharmacodynamic profile. *Clin Pharmacokinet*. 1999;37(3):177-193.

28. Korprasertthaworn P, Polasek TM, Sorich MJ, et al. In vitro characterization of the human liver microsomal kinetics and reaction phenotyping of olanzapine metabolism. *Drug Metab Dispos*. 2015;43(11):1806-1814.

29. Bigos KL, Pollock BG, Coley KC, et al. Sex, race, and smoking impact olanzapine exposure. *J Clin Pharmacol*. 2008;48(2):157-165.

30. Davies SJ, Mulsant BH, Flint AJ, et al. The impact of sertraline co-administration on the pharmacokinetics of olanzapine: a population pharmacokinetic analysis of the STOP-PD. *Clin Pharmacokinet*. 2015;54(11):1161-1168.

31. US Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Veterinary Medicine (CVM). Bioanalytical Method Validation: Guidance for Industry. https://www.fda.gov/files/drugs/published/Bioanalytical-Method-Validation-Guidance-for-Industry.pdf. Published May 2018. Accessed 23 January 2019.

32. Keizer RJ, van Benten M, Beijnen JH, Schellens JH, Huitema AD. Pirana and PCluster: a modeling environment and cluster infrastructure for NONMEM. *Comput Methods Programs Biomed*. 2011;101(1):72-79.

33. Lindbom L, Ribbing J, Jonsson EN. Perl-speaks-NONMEM (PsN)—a Perl module for NONMEM related programming. *Comput Methods Programs Biomed*. 2004;75(2):85-94.

34. Sarkar D. *Lattice: Multivariate Data Visualization with R*. New York, NY: Springer; 2008.

35. Wickham H. *ggplot2: Elegant Graphics for Data Analysis*. New York, NY: Springer-Verlag; 2009.

36. Wilke CO. cowplot: Streamlined Plot Theme and Plot Annotations for 'ggplot2'. R package version 092, 2017. https://wilkelab.org/cowplot/. Accessed 24 January 2020.

37. Jonsson EN, Karlsson MO. Xpose—an S-PLUS based population pharmacokinetic/pharmacodynamic model building aid for NONMEM. *Comput Methods Programs Biomed*. 1999;58(1):51-64.

38. Holford N, Heo YA, Anderson B. A pharmacokinetic standard for babies and adults. *J Pharm Sci*. 2013;102(9):2941-2952.

39. Al-Sallami HS, Goulding A, Grant A, Taylor R, Holford N, Duffull SB. Prediction of fat-free mass in children. *Clin Pharmacokinet*. 2015;54(11):1169-1178.

40. Peters AM, Snelling HL, Glass DM, Bird NJ. Estimation of lean body mass in children. *Br J Anaesth*. 2011;106(5):719-723.

41. Centers for Disease Control and Prevention (CDC). BMI-for-age charts, 2 to 20 years, LMS parameters and selected smoothed BMI (kilograms/meters squared) percentiles, by sex and age. https://www.cdc.gov/growthcharts/percentile_data_files.htm. Accessed 24 January 2020.

42. Petty F, Brannan S, Casada J, et al. Olanzapine treatment for post-traumatic stress disorder: an open-label study. *Int Clin Psychopharmacol*. 2001;16(6):331-337.

43. Yanai T, Iwasa S, Hashimoto H, et al. A double-blind randomized phase II dose-finding study of olanzapine 10 mg or 5 mg for the prophylaxis of emesis induced by highly emetogenic cisplatin-based chemotherapy. *Int J Clin Oncol*. 2018;23(2):382-388.

44. Attia E, Steinglass JE, Walsh BT, et al. Olanzapine versus placebo in adult outpatients with anorexia nervosa: a randomized clinical trial. *Am J Psychiatry*. 2019;176(6):449-456.

45. IBM Micromedex®. Olanzapine. Greenwood Village (CO): Truven Health Analytics. Available from: www.micromedexsolutions.com. Subscription required to view. Accessed 30 January 2020.

46. Gossen D, de Suray JM, Vandenhende F, Onkelinx C, Gangji D. Influence of fluoxetine on olanzapine pharmacokinetics. *AAPS PharmSci*. 2002;4(2):E11.

47. Sathirakul K, Chan C, Teng L, Bergstrom RF, Yeo KP, Wise SD. Olanzapine pharmacokinetics are similar in Chinese and Caucasian subjects. *Br J Clin Pharmacol*. 2003;56(2):184-187.

48. Shirley KL, Hon YY, Penzak SR, Lam YW, Spratlin V, Jann MW. Correlation of cytochrome P450 (CYP) 1A2 activity using caffeine phenotyping and olanzapine disposition in healthy volunteers. *Neuropsychopharmacology*. 2003;28(5):961-966.

49. Chow SC. Bioavailability and bioequivalence in drug development. *Wiley Interdiscip Rev Comput Stat*. 2014;6(4):304-312.

50. Food and Drug Administration (FDA). Olanzapine Pamoate (Zyprexa). Clinical Pharmacology/Biopharmaceutics Review: Pharmacometric Review (22–173). https://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/022173s000ClinPharmR.pdf. Submitted 11 March 2009. Accessed 24 January 2020.

51. Bonate PL. *Pharmacokinetic-Pharmacodynamic Modeling and Simulation*. Second ed. New York, NY: Springer Science; 2011.

52. Mahmood I. Theoretical versus empirical allometry: facts behind theories and application to pharmacokinetics. *J Pharm Sci*. 2010;99(7): 2927-2933.

53. Holford NH, Anderson BJ. Why standards are useful for predicting doses. *Br J Clin Pharmacol*. 2017;83(4):685-687.

54. Greeley WJ, de Bruijn NP, Davis DP. Sufentanil pharmacokinetics in pediatric cardiovascular patients. *Anesth Analg*. 1987;66(11):1067-1072.

55. National Library of Medicine (US). Label: Sufentanil Citrate Injection in DailyMed. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=95e639db-1ca3-4328-b347-7ea348f6cc72. Accessed 27 April 2020.

56. Sagreiya H, Chen YR, Kumarasamy NA, Ponnusamy K, Chen D, Das AK. Differences in antipsychotic-related adverse events in adult, pediatric, and geriatric populations. *Cureus*. 2017;9(2):e1059.

57. Harvey EJ, Flanagan RJ, Taylor DM. The preparation and stability of a liquid olanzapine preparation for oral administration in hospitals. *Pharm J*. 2000;265(7110):275-276.

58. San L, Casillas M, Ciudad A, Gilaberte I. Olanzapine orally disintegrating tablet: a review of efficacy and compliance. *CNS Neurosci Ther*. 2008;14(3):203-214.

59. Wang CY, Zhang ZJ, Li WB, et al. The differential effects of steady-state fluvoxamine on the pharmacokinetics of olanzapine and clozapine in healthy volunteers. *J Clin Pharmacol*. 2004;44(7): 785-792.

SUPPORTING INFORMATION

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