

Population Pharmacokinetics of Viloxazine Extended-Release Capsules in Pediatric Subjects With Attention Deficit/Hyperactivity Disorder

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Abstract

Viloxazine extended-release capsules (viloxazine ER; Qelbree) is a novel nonstimulant, recently approved by the US Food and Drug Administration for the treatment of ADHD in pediatrics. Here, we characterize the pharmacokinetics (PK) of viloxazine and its major metabolite, 5-HVLX-gluc, using a population PK model and evaluate the impact of 1–4 days of missed viloxazine ER doses on viloxazine PK. Data from 4 phase 3 trials in pediatric subjects treated with viloxazine ER were used to establish the PK model. Covariate analysis was conducted on the final base model. The impact of 1–4 days of missed doses on steady-state viloxazine PK was evaluated using Monte Carlo simulations. A 1-compartmental linear model with first-order absorption and elimination of the parent drug and first-order metabolite formation and elimination properly described the population PK of viloxazine and 5-HVLX-gluc. Body weight impacted the systemic exposure of viloxazine and 5-HVLX-gluc. Predicted PK parameters at steady state (mean \pm standard deviation) in children receiving viloxazine ER were determined. C_{\max} was $1.60 \pm 0.70 \mu\text{g/mL}$ at 100 mg, $2.83 \pm 1.31 \mu\text{g/mL}$ at 200 mg, and $5.61 \pm 2.48 \mu\text{g/mL}$ at 400 mg. AUC_{0-t} was $19.29 \pm 8.88 \mu\text{g}\cdot\text{h/mL}$ at 100 mg, $34.72 \pm 16.53 \mu\text{g}\cdot\text{h/mL}$ at 200 mg, and $68.00 \pm 28.51 \mu\text{g}\cdot\text{h/mL}$ at 400 mg. PK parameters for adolescents receiving viloxazine ER were also determined. C_{\max} was $2.06 \pm 0.90 \mu\text{g/mL}$ at 200 mg, $4.08 \pm 1.67 \mu\text{g/mL}$ at 400 mg, and $6.49 \pm 2.87 \mu\text{g/mL}$ at 600 mg. AUC_{0-t} was $25.78 \pm 11.55 \mu\text{g}\cdot\text{h/mL}$ at 200 mg, $50.80 \pm 19.76 \mu\text{g}\cdot\text{h/mL}$ at 400 mg, and $79.97 \pm 36.91 \mu\text{g}\cdot\text{h/mL}$ at 600 mg. Simulations revealed that, regardless of the duration of the dosing interruption, viloxazine concentration returned to steady-state levels after approximately 2 days of once-daily dosing of viloxazine ER.

Keywords

ADHD, drug holiday, pharmacokinetics, population PK, SPN-812, viloxazine

Viloxazine is a structurally distinct molecule with demonstrated activity in the noradrenergic and serotonergic systems.¹ A novel version, viloxazine extended-release capsules (viloxazine ER), has been recently approved by the US Food and Drug Administration under the trade name Qelbree as a nonstimulant treatment for attention deficit/hyperactivity disorder (ADHD) in children and adolescents. In 4 recent phase 3 trials, once-daily viloxazine ER was well tolerated over 6 to 8 weeks of treatment ($n = 1117$), with a low rate of discontinuations because of adverse events (fewer than 4% across all trials).^{2–7} In 3 of these 4 trials, statistically significant improvements in the primary end point were reported as quickly as 1 week following the onset of treatment, relative to placebo.^{2–6} Analyses evaluating the pharmacodynamic effects of viloxazine ER within the therapeutic range have found no clear dose-response relationship on measures of either safety or efficacy (data on file). This is not surprising considering that many psychiatric treatments have demonstrated weak, if any, dose-

response relationships on a variety of outcome measures.^{8,9}

In vivo absorption-distribution-metabolism-excretion studies demonstrated that the major metabolic route in humans is 5-hydroxylation mediated by cytochrome P450 (CYP) 2D6, with minor involvement from CYP1A2, CYP2B6, CYP2C9,

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CYP2C19, and CYP3A4. Of these CYP enzymes, CYP2D6 is thought to be responsible for less than 50% of 5-hydroxyviloxazine, with subsequent glucuronidation to 5-HVLX-gluc (viloxazine's major metabolite) mediated by uridine 5'-diphosphoglucuronosyltransferase 1A9 and 2B15.¹⁰ Viloxazine forms a unique N-carbamoyl glucuronide in humans, the chemical reactivity characteristics of which are similar to stable glucuronide conjugates and dissimilar to acyl glucuronides; therefore, it is a stable phase II conjugate.¹⁰ Viloxazine is rapidly metabolized and excreted in urine, with no known active metabolites.¹⁰ In vitro drug-drug interaction testing has shown that viloxazine is not a significant inhibitor or inducer of CYP isoenzymes, except for being a strong inhibitor of CYP1A2.¹⁰

Viloxazine metabolism is not thought to rely solely on CYP2D6; alternatively, metabolism switching using multiple alternative CYP enzyme pathways may be activated if the major pathway is inhibited or not fully active. These alternative pathways are likely to modulate the impact on CYP2D6 activity.¹⁰ These in vitro data are consistent with a recent clinical drug interaction study in which CYP2D6 inhibition by paroxetine, a strong CYP2D6 inhibitor, resulted in a less than 35% increase in systemic viloxazine exposure, as measured by AUC.¹¹ Furthermore, another clinical study found only minimal impact of CYP2D6 genetic polymorphisms on systemic viloxazine exposure: C_{max} increased only 20% and AUC_{0-24} increased 25% in poor CYP2D6 metabolizers, relative to extensive (normal) metabolizers.¹²

Model-based population pharmacokinetic (PK) approaches can provide insight into how intrinsic (eg, CYP polymorphisms, body weight) and extrinsic (eg, polypharmacy, missed doses) factors might influence drug exposure.¹³ Excess variability in drug exposure can result in significant changes to a drug's efficacy or safety profile, particularly in drugs with a narrow therapeutic index. Having been shown to be safe at high doses^{4,5,11,14-16} and effective at improving ADHD symptoms and functional impairments even at lower doses,^{2,3,17} viloxazine ER is thought to have a wide therapeutic window. However, even in drugs generally considered safe, drug exposure can be heavily influenced by missed or forgotten doses, body weight, body mass index (BMI), or factors altering hepatic metabolism. Therefore, it is crucial for clinicians to consider potential sources of variability as well as an individual drug's capacity for forgiveness (ie, the number of consecutive doses that can be missed without efficacy or safety consequences) when making treatment decisions.

To develop a population PK model for viloxazine, the present analyses used pooled data from 4 phase 3 clinical trials examining the efficacy and tolerability

of viloxazine ER in the treatment of children and adolescents with ADHD.²⁻⁵ During these studies, sparse blood samples (up to 5 samples per subject) were collected to characterize the population PK of viloxazine and its major metabolite (5-hydroxyviloxazine glucuronide [5-HVLX-gluc]) at 4 viloxazine ER doses (100, 200, 400, and 600 mg/day). Therefore, the objectives of the present study were to (1) characterize the population PK of viloxazine and its metabolite, 5-HVLX-gluc, in children (6-11 years old) and adolescents (12-17 years old) with ADHD while simultaneously testing for covariates to identify potential sources of variability; and (2) evaluate the impact of missed doses of viloxazine ER on viloxazine steady-state PK.

Methods

Data Source

The study protocols and any amendments were approved by the Advarra Institutional Review Board (IRB) and conducted in accordance with the Helsinki Declaration and the International Council for Harmonisation Good Clinical Practice guidelines. Three study sites also submitted materials to a local IRB: Institutional Review Board of the Mount Sinai School of Medicine (New York, New York), Johns Hopkins Institutional Review Boards (Baltimore, Maryland), Institutional Review Board of Penn State College of Medicine (Hershey, Pennsylvania). Children provided informed assent, and the parent(s) or legal guardian(s) provided written informed consent to allow their child's participation prior to any study-related procedures.

The analyses were conducted using PK data collected in 4 phase 3 multicenter randomized, double-blind, placebo-controlled, 3-arm parallel-group studies designed to assess the efficacy and safety of viloxazine ER as monotherapy in the treatment of pediatric patients with ADHD; details of the studies and study populations are described elsewhere.²⁻⁵ For all 4 studies, optional blood samples were collected to assess viloxazine and 5-HVLX-gluc PK. A total of 5 blood samples were drawn between visits 3 and 10: predose and 1, 2, 4, and 6 hours postdose at steady state. On the day the predose sample was taken, study medication was administered at the site visit. Postdose samples were allowed to be drawn on the same day or alternative visit days. If drawn on alternate visit days, the time the study medication was taken that day was required to be consistent with the dose time for the previous 2 days, and the time of dose administration was required to be recorded for all 3 days. Blood samples were obtained using only sparse, flexible sampling, and thus, data are reported by the day and time of sample collection.

Studies P301² (NCT03247530) and P303⁴ (NCT03247543) were conducted in children

(6-11 years old). In study P301, after randomization to either placebo, 100 mg/day, or 200 mg/day, children underwent 1 week of titration followed by 5 weeks of maintenance, for a total of 6 weeks of treatment. The optional PK samples were collected between weeks 2 and 6 (inclusive). In study P303, after randomization to either placebo, 200 mg/day, or 400 mg/day, children underwent 3 weeks of titration followed by 5 weeks of maintenance, for a total of 8 weeks of treatment. The optional sparse PK samples were collected between weeks 3 and 8 (inclusive).

Studies P302³ (NCT03247517) and P304⁵ (NCT03247556) were conducted in adolescents (12-17 years old). In study P302, after randomization to either placebo, 200 mg/day, or 400 mg/day, adolescents underwent 1 week of titration followed by 5 weeks of maintenance, for a total of 6 weeks of treatment. The optional PK samples were collected between weeks 1 and 6 (inclusive). In study P304, after randomization to either placebo, 400 mg/day, or 600 mg/day, adolescents underwent 2 weeks of titration followed by 5 weeks of maintenance, for a total of 7 weeks of treatment. The optional sparse PK samples were collected between weeks 1 and 7 (inclusive).

Blood Sample Analysis

A total of 495 subjects randomized to viloxazine ER treatment had sufficient PK samples to be included in the population PK analysis data set: 86 subjects treated at the 100-mg dose, 197 subjects treated at the 200-mg dose, 164 subjects treated at the 400-mg dose, and 48 subjects treated at the 600-mg dose. Plasma concentrations of viloxazine and 5-HVLX-gluc were determined using validated liquid chromatography with tandem mass spectrometry (methods described in detail elsewhere^{15,16}). The lower limit of quantification was 0.01 $\mu\text{g/mL}$ for viloxazine and 0.005 $\mu\text{g/mL}$ for 5-HVLX-gluc.

Population Pharmacokinetic Analysis

The population PK base model was developed to simultaneously describe the concentrations of viloxazine (the parent drug) and 5-HVLX-gluc (its primary metabolite). The rationale for model selection was based on the inspection of the linear and log-linear plots of viloxazine and 5-HVLX-gluc concentrations versus time and on prior knowledge of viloxazine PK.¹⁸ During PK model development, which describes parent and metabolite plasma concentrations, assumptions are made because the model simultaneously describing viloxazine and 5-HVLX-gluc PK is unidentifiable a priori.¹⁹ To address these identifiability issues, the values of the volume of distribution of viloxazine and 5-HVLX-gluc were assumed to be identical.

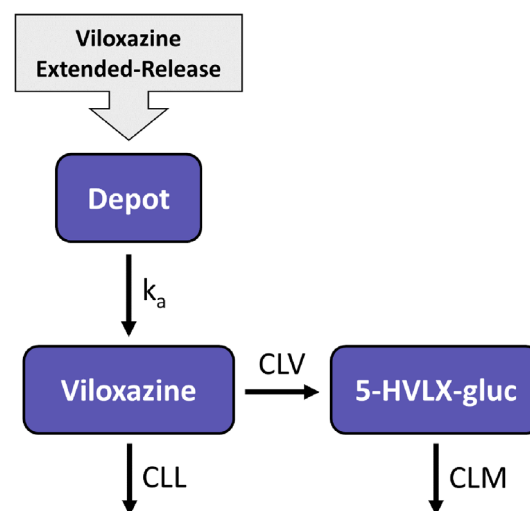


Figure 1. Schematic representation of the PK model for viloxazine and 5-HVLX-gluc. Viloxazine was well represented by a 1-compartment model with first-order absorption and elimination of the parent drug and first-order metabolite formation and elimination. CLL, viloxazine clearance; CLV, viloxazine metabolic clearance; CLM, 5-HVLX-gluc clearance; k_a , viloxazine absorption rate constant.

The first-order conditional estimate with interaction method was used for parameter estimation. The appropriateness of the model was evaluated using various goodness-of-fit criteria, including diagnostic scatterplots, likelihood ratio test, and measures of model stability and adequacy (ie, successful convergence, significant digits, matrix singularity). When comparing alternative nested models, the results for the likelihood ratio test were considered statistically significant if decreases in the objective function value (OFV) were greater than 3.84 ($P < .05$, degrees of freedom [df] = 1) throughout the model-building process. Interindividual variability of all the model parameters was assumed to be lognormally distributed. Residual variability was modeled using a combined (additive and proportional) error.

The model used in the population PK analysis was a 1-compartment model with first-order absorption and elimination of the parent drug and first-order metabolite formation and elimination, as shown in Figure 1. For full concentration-over-time plots over 72 hours, see recently reported studies in healthy adults.^{11,15,16}

Bioavailability (F) was assumed to be equal to 1. The following parameters were used to jointly describe the viloxazine and 5-HVLX-gluc concentrations: the apparent volume of distribution of viloxazine ($V2/F$), the apparent volume of distribution of 5-HVLX-gluc ($V3/F$), the viloxazine absorption rate constant (k_a), the viloxazine clearance (CLL), the viloxazine metabolic clearance (CLV), and the 5-HVLX-gluc clearance (CLM). $V2/F$, and $V3/F$ were assumed to be identical to address identifiability issues.

Covariate Analysis

We used scientific rationale combined with graphical and statistical approaches to identify which covariates to examine with respect to their potential influence on the PK parameters of viloxazine and 5-HVLX-gluc. The following variables were included in the covariate analyses based on prior knowledge of their potential to influence systemic drug exposure: age, height, weight, BMI, sex, race, ethnicity, alanine aminotransferase, aspartate aminotransferase, and creatinine. CYP2D6 genetic polymorphism was not included as a covariate because of recent data demonstrating only a minor impact of CYP2D6 polymorphisms on systemic viloxazine exposure.^{12,20} Moreover, coadministration of viloxazine with the strong CYP2D6 inhibitor paroxetine moderately affected viloxazine's PK profile.¹¹ Based on these data, subjects were not genotyped for their CYP2D6 enzyme activity (phenotype) in these phase 3 studies. Covariate model building was a stepwise process consisting of a forward and a backward selection procedure.

Empirical Bayesian estimates of individual parameters were obtained from the best-performing model in the population PK analysis. A descriptive analysis was conducted to explore the potential impact of the covariates on the best-performing model parameters as a function of the individual parameter estimates. The covariates selected as potentially informative (in this initial analysis, body weight and age) were formally evaluated using a stepwise process.²¹

The relationship between the typical values of model parameters and covariates (body weight and age) was formally tested using the following relationship:

$$P = P_{ref} \left(\frac{Cov}{typCov} \right)^g$$

where P is the model parameter, typCov is the typical value of the selected covariates in the study population (set to the medians: body weight, 36.35 kg, age, 11 years), P_{ref} is the value of the model parameter when the covariate equals the median population value, and g is the parameter characterizing the shape of the response.

Initially, each covariate was individually included in the model to identify significant covariates, in which significance was defined a priori as a reduction in the OFV of ≥ 6.64 ($P < .01$, $df = 1$). Next, the significant covariates and/or those considered clinically important were added to the base model 1 covariate into 1 PK parameter at a time. The most significant covariate was included into the model first. This new model served as a new starting model for the next iteration. The test of significance and adding-on step was repeated until all significant covariates were included. A backward

elimination process was then followed. First, the effect of the covariate was assumed to significantly contribute to the model if the OFV increased by more than 10.83 ($P < .001$, $df = 1$) on removal of that covariate. After evaluating the impact of all variables in the full model, the covariate with the smallest nonsignificant effect on the OFV was removed from the model. This process was repeated until all remaining variables significantly contributed to the model's ability to describe the data. The model resulting from the backward process was considered the final model.

Model Diagnostics and Model Performance

Goodness-of-fit plots were generated for evaluating the results of model fitting. These plots included: (1) the observed concentrations versus individual and population-predicted concentrations, (2) the absolute individual weighed residuals versus individual predictions, and (3) the conditional weighted residuals versus time.

Model performance/validation and stability were assessed using visual predictive checks (VPCs). The VPC method evaluated the adequacy of the final model, including the effects of statistically significant covariates. This assumes that parameter uncertainty is negligible relative to interindividual variability and residual error. The basic premise is that a model and parameters derived from an observed data set should produce simulated data that are similar to the original observed data. In cases in which significant covariates were detected, the VPCs were stratified according to the covariates retained.

In the VPC analysis, the PK concentrations of 100 subjects were simulated based on the final model, and a 90% prediction interval was computed based on the simulated values. The observed concentrations versus time were plotted on the prediction interval to visually assess the concordance between the simulated and observed data. The distributions of quantiles (5th, 50th [median], and 95th) of simulated data were compared graphically with the quantiles of observed data.

Bootstrap analysis was conducted for calculating bias, standard errors and confidence intervals of parameter estimates. To this end, 100 data sets sampled with replacement from the original data set were generated, and the model was fitted to each new data set. Statistics on the PK parameters estimated in the 100 runs are reported.

Impact of Missed Doses of Viloxazine ER on Viloxazine Pharmacokinetics

Plasma concentration peaks and troughs resulting from missed doses can result in efficacy and safety consequences for patients. To this end, the impact of missed viloxazine ER doses on viloxazine PK was estimated

Table 1. Descriptive Statistics of the Demographic and Laboratory Variables Included in the Covariate Analysis

Variable	Overall 6-17 Years n = 495	Children 6-11 Years n = 263	Adolescents 12-17 Years n = 232
Age, y	11.2 ± 3.1	8.7 ± 1.7	14.0 ± 1.6
Height, cm	149.0 ± 17.9	135.9 ± 11.7	163.9 ± 10.6
Weight, kg	44.5 ± 16.5	32.8 ± 8.9	57.7 ± 12.7
BMI, kg/m ²	19.3 ± 3.4	17.5 ± 2.4	21.3 ± 3.3
Sex			
Males	337 (68.08%)	179 (68.08%)	158 (68.10%)
Females	158 (31.92%)	84 (31.94%)	74 (31.90%)
Race			
White	258 (52.12%)	121 (46.01%)	137 (59.05%)
Black or African American	214 (43.23%)	125 (47.53%)	89 (38.36%)
Other	23 (4.64%)	17 (6.46%)	6 (2.59%)
Ethnicity			
Hispanic/Latino	112 (22.63%)	59 (22.43%)	53 (22.84%)
Non-Hispanic or non-Latino	383 (77.37%)	204 (77.57%)	179 (77.16%)
ALT, U/L (range, 5-30 U/L)	15 ± 7	15 ± 7	15 ± 8
AST, U/L (range, 0-41 U/L)	24 ± 6	26 ± 6	22 ± 7
Creatinine, mg/dL (range, 0.24-1.20 mg/dL)	0.59 ± 0.17	0.50 ± 0.09	0.69 ± 0.19

ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Means ± standard deviation or n (%).

using Monte Carlo simulations from the final population PK model previously presented (ie, children and adolescents treated with various viloxazine ER doses).

Simulations were conducted for each dose level (ie, daily doses of 100, 200, 400, and 600 mg) during 10 days of viloxazine ER dosing followed by an off-drug holiday period (ie, skipped dosing) of 1, 2, 3, and 4 days, with dosing resuming immediately after each off-drug period for an additional 10 consecutive viloxazine ER doses. Because weight was retained from the primary model as a significant covariate affecting viloxazine exposure, these simulations were stratified by the median body weight in children (31.5 kg) and adolescents (57.25 kg).

Software

Data preparation, summary statistics, and reports were performed using R (version 4.0.0).²² The population PK analysis was conducted using NONMEM software, version 7.4.²³ NONMEM was executed in a Windows 10 operating system using the Fortran compiler gfortran version 4.6.0. The Perl-based software PsN was used for bootstrapping.²⁴

Results

Subject Characteristics

The mean age of the 495 subjects included in the analysis was 11 years (range, 6-17 years), and the mean body weight was 44 kg (range, 20-92.5 kg). The majority of the subjects were male (n = 337, 68%; female, n = 158, 32%), either white (n = 258, 52%) or black/African American (n = 214, 43%), and

not Hispanic or Latino (n = 383, 77%). Descriptive statistics of the demographic and laboratory data used in the covariate analyses are presented in Table 1 for the total population, children (6-11 years), and adolescents (12-17 years).

Population Pharmacokinetic Model and Covariate Analysis

A base model was initially developed to simultaneously fit viloxazine and 5-HVLX-gluc concentrations. The model was a 1-compartment model with first-order absorption and elimination of the parent drug, and first-order metabolite formation and elimination as shown in Figure 1.

Empirical Bayesian estimates of individual parameters were obtained from the population PK analysis. The relationship between individual model parameters and selected covariates was initially explored graphically. This analysis indicated a potential effect of BMI, body weight, and age on model parameters. Given the collinearity between BMI and body weight (confirmed by Pearson correlation, $r = 0.87$, $P < .0001$) and the clinical relevance of body weight, body weight was selected for a formal model-based covariate assessment. A highly significant correlation was also detected between body weight and age ($r = 0.84$, $P < .0001$). Therefore, the joint impact of age and body weight on the model parameters was preliminarily explored in the covariate screening procedure.

All intermediate models tested are listed in the supplementary materials, Table S1, in the chronological order in which they were evaluated. The first column

Table 2. Population PK Parameter Model Estimates and Bootstrap Analysis Results

Parameter	Model Estimate ^a	Bootstrap ^b
Fixed effect		
V2/F, L	14.60 ± 0.67 (4.60%)	14.57 (14.42-14.73)
CLL, L/h	0.87 ± 0.18 (21.30%)	0.85 (0.80-0.90)
k _a , 1/h	0.068 ± 0.0028 (4.10%)	0.068 (0.0662-0.0697)
CLV, L/h	4.72 ± 0.21 (4.40%)	4.77 (4.71-4.82)
CLM, L/h	6.75 ± 0.31 (4.60%)	6.85 (6.77-6.93)
WT, V	0.78 ± 0.08 (10.40%)	0.76 (0.74-0.78)
WT, CLV	0.59 ± 0.07 (12.00%)	0.58 (0.56-0.6)
WT, CLM	0.70 ± 0.07 (9.40%)	0.69 (0.67-0.70)
Random effect		
V2/F, L	0.10 ± 0.03 (28.00%)	0.12 (0.11-0.14)
CLL, L/h	3.03 ± 0.50 (16.40%)	3.20 (3.08-3.32)
k _a , 1/h	0.1700 ± 0.0266 (15.60%)	0.1706 (0.1525-0.1847)
CLV, L/h	0.11 ± 0.01 (11.40%)	0.11 (0.11-0.12)
CLM, L/h	0.08 ± 0.01 (14.90%)	0.08 (0.08-0.08)
Residual error		
Additive	0.12 ± 0.01 (5.50%)	0.12 (0.12-0.13)
Proportional	0.29 ± 0.01 (3.50%)	0.29 (0.28-0.29)

CLL, viloxazine clearance; CLM, 5-HVLX-gluc clearance; CLV, viloxazine metabolic clearance; h, hour; k_a, viloxazine absorption rate constant; L, liter; V, volume of distribution; V2/F, apparent volume of distribution for viloxazine; WT, weight.

^a Model estimates are reported as mean ± standard error (percent relative standard error).

^b Bootstrap values are reported as mean (95% confidence intervals of the parameter estimates).

identifies the model tested; the second column lists the reference model run to which the test model run was compared; the third and fourth columns list the OFV for each test run and the change in OFV from the reference run (test – reference), respectively; the fifth column briefly describes the hypothesis or objective that was tested by the model; and the last column describes the conclusion based on the chi-square statistic.

The effect of body weight on V2/F, CLM, and CLV (model 10) was found to be statistically significant ($P < .01$, $df = 1$) during the forward addition model step. The relationship between body weight and V2/F was removed from model 10 in the backward elimination procedure. The removal of this covariate was associated with an increase in the OFV of 60.74 units (model 13). As a result, model 10 was considered the final model.

Final Model Evaluation

PK parameter estimates resulting from the final population PK base model and the bootstrapping procedure are presented in Table 2. These 2 estimates demonstrate good agreement and add further support for the accuracy of the model. The goodness-of-fit diagnostic plots for the final model are shown in Figure S1 in the supplemental material. Overall, there was no apparent bias in these diagnostic plots, suggesting that the model

was adequate for simultaneously describing the PK of viloxazine and 5-HVLX-gluc.

The VPCs were stratified by age to assess the stability and the model performance for children and adolescents given the lower body weight in children (median, 31.5 kg; Figure 2A) versus adolescents (median, 57.3 kg; Figure 2B). The VPCs indicated that the model performed well in both children and adolescents. The median PK values as well as the dispersion of the data around the median were well described by the 5th, 50th (median), and 95th percentiles, indicating that the population model properly described the observed data. For brevity, only the 200- and 400-mg doses are shown in Figure 2; the remaining doses are shown in Figures S2 and S3 in the supplemental materials.

Additional simulations were conducted to explore the impact of body weight in children and adolescents on the expected viloxazine exposure. The population PK model parameters were used to estimate the individual exposure of viloxazine at steady state using an empirical Bayesian parameter estimation approach. A noncompartmental analysis approach was then applied to the individual exposure to estimate the steady-state PK parameter values. The estimated steady-state exposure values of viloxazine estimated by the C_{max} , C_{min} , C_{avg} , T_{max} , AUC_{0-t} , $t_{1/2}$, K_{el} , CL/F , V/F , and fluctuation (%) parameters at each of the 4 doses are presented in Table 3. The comparison of the estimated exposure at steady state indicated that viloxazine exposure increases proportionally with dose and inversely with body weight (ie, viloxazine exposure increases as body weight decreases).

Predicted viloxazine parameters at steady state ± standard deviation (SD) were as follows: C_{max} at 100-, 200-, 400-, and 600-mg daily doses of viloxazine ER was $1.60 ± 0.70$, $2.83 ± 1.31$, $5.61 ± 2.48$, and $8.89 ± 4.23$ $μg/mL$, respectively, in children and $1.16 ± 0.46$, $2.06 ± 0.90$, $4.08 ± 1.67$, and $6.49 ± 2.87$ $μg/mL$, respectively, in adolescents. Similarly, estimated viloxazine AUC_{0-t} at 100-, 200-, 400-, and 600-mg daily doses of viloxazine ER in children was $19.29 ± 8.88$, $34.72 ± 16.53$, $68.00 ± 28.51$, and $106.96 ± 52.20$ $μg·h/mL$, respectively, in children and $14.15 ± 6.10$, $25.78 ± 11.55$, $50.80 ± 19.76$, and $79.97 ± 36.91$ $μg·h/mL$, respectively, in adolescents. Viloxazine CL/F did not differ by dose and increased only slightly with body weight: at 100 and 600 mg viloxazine ER, estimated CL/F ranged from $6.29 ± 6.89$ to $6.60 ± 5.66$ L/h, respectively, in children, and $7.88 ± 7.01$ to $8.11 ± 5.95$ L/h, respectively, in adolescents. The correlation of body weight with predicted V2/F, CLL, CLV, and CLM is shown in Figure 3. The relationships between viloxazine ER dose and AUC , C_{max} , and CL/F are shown in Figure 4. Except for CL/F , C_{max} and AUC

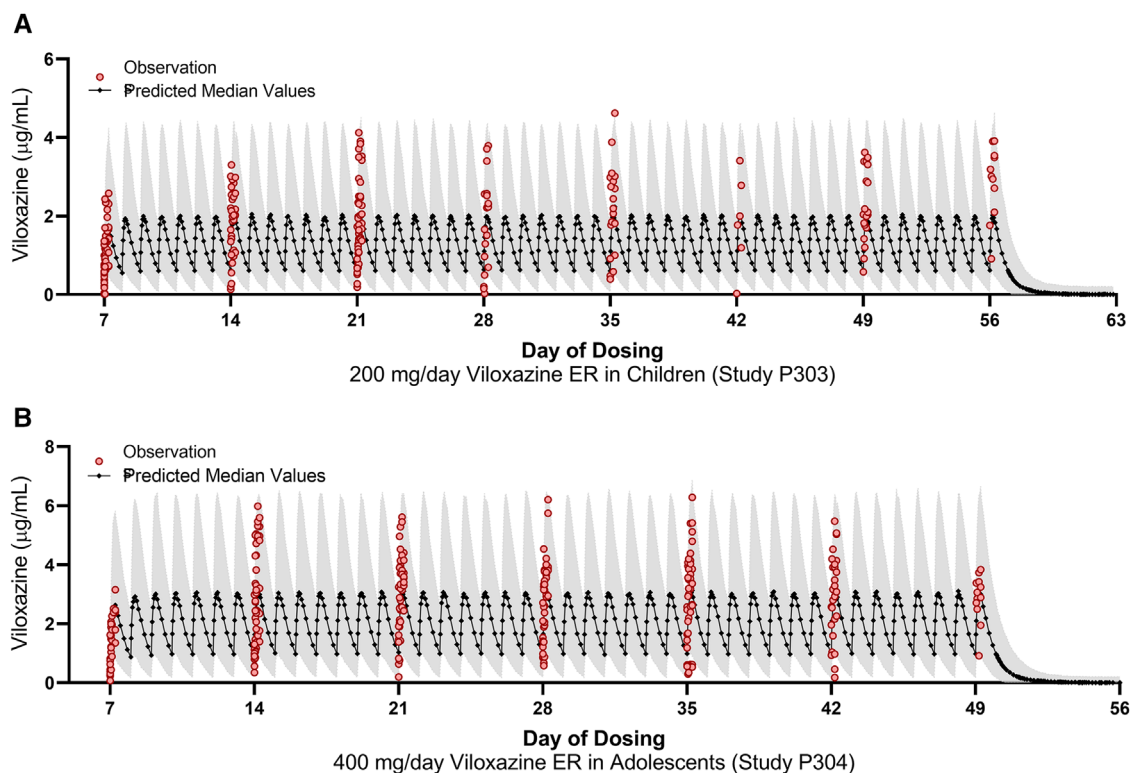


Figure 2. Visual predictive checks. Observed and predicted viloxazine concentrations in children from study P303 (A) and adolescents from study P304 (B) administered viloxazine extended-release at 200 and 400 mg/day, respectively. Individual observed values are represented by red-filled circles, the median predicted values are represented by black diamonds and connected by the black lines, and the shaded light-gray area represents the 90% prediction interval. Visual predictive checks for all studies and doses in children and adolescents are shown in Figures S2 and S3, respectively, in the supplemental materials.

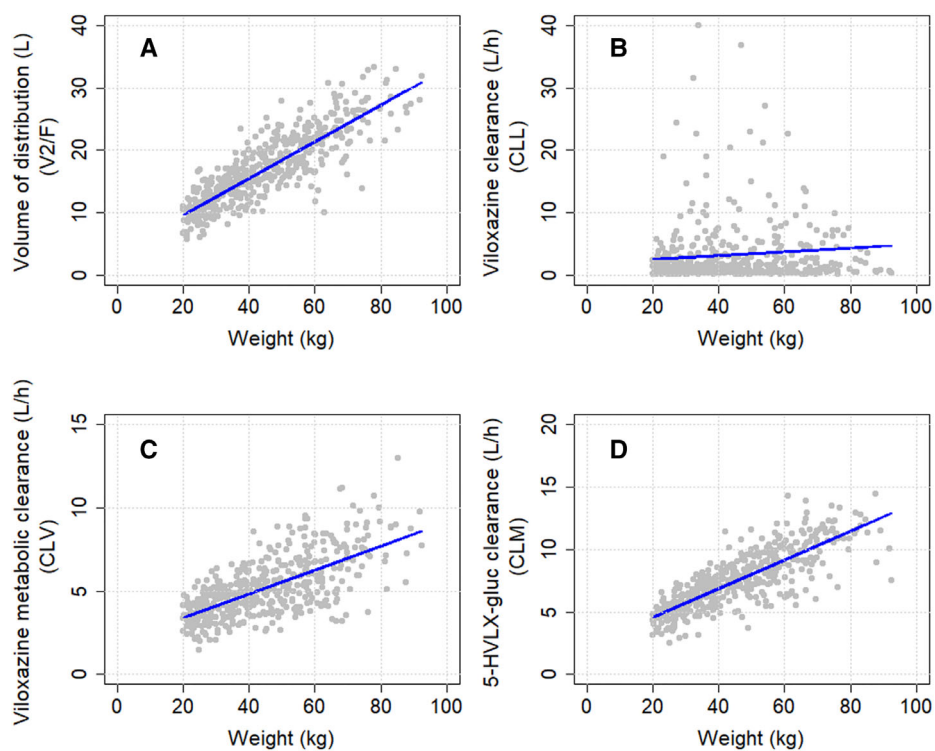


Figure 3. Correlation of body weight with PK parameters. Correlation of body weight (in kilograms) with predicted volume of distribution (A), viloxazine clearance (B), viloxazine metabolic clearance (C), and 5-HVLX-gluc clearance (D).

Table 3. Estimated Steady-State Viloxazine Parameters for Children and Adolescents

Dose	Parameter	Children	Adolescents	
100 mg	Body weight, kg (median)	31.50	57.25	
	C_{max} , $\mu\text{g/mL}$	1.60 ± 0.70	1.16 ± 0.46	
	C_{min} , $\mu\text{g/mL}$	0.21 ± 0.20	0.14 ± 0.15	
	C_{avg} , $\mu\text{g/mL}$	0.80 ± 0.37	0.59 ± 0.25	
	T_{max} , h	4.50 (1.00-20.00)	5.00 (1.00-20.00)	
	AUC_{0-t} , $\mu\text{g}\cdot\text{h/mL}$	19.29 ± 8.88	14.15 ± 6.10	
	$t_{1/2}$, h	8.13 ± 5.47	7.91 ± 7.11	
	K_{el} , 1/h	0.13 ± 0.12	0.16 ± 0.17	
	CL/F , L/h	6.29 ± 6.89	7.88 ± 7.01	
	V/F , L	61.77 ± 62.16	71.59 ± 64.93	
	Fluctuation, %	189.62 ± 81.01	189.46 ± 77.55	
	200 mg	C_{max} , $\mu\text{g/mL}$	2.83 ± 1.31	2.06 ± 0.90
		C_{min} , $\mu\text{g/mL}$	0.49 ± 0.40	0.36 ± 0.29
C_{avg} , $\mu\text{g/mL}$		1.45 ± 0.69	1.07 ± 0.48	
T_{max} , h		4.00 (1.00-12.00)	5.00 (1.00-16.00)	
AUC_{0-t} , $\mu\text{g}\cdot\text{h/mL}$		34.72 ± 16.53	25.78 ± 11.55	
$t_{1/2}$, h		9.60 ± 5.97	9.83 ± 6.30	
K_{el} , 1/h		0.11 ± 0.09	0.11 ± 0.10	
CL/F , L/h		6.41 ± 5.76	7.95 ± 6.02	
V/F , L		69.71 ± 49.03	88.70 ± 53.94	
Fluctuation, %		171.03 ± 53.90	168.15 ± 53.59	
400 mg		C_{max} , $\mu\text{g/mL}$	5.61 ± 2.48	4.08 ± 1.67
		C_{min} , $\mu\text{g/mL}$	0.94 ± 0.63	0.700 ± 0.47
		C_{avg} , $\mu\text{g/mL}$	2.83 ± 1.19	2.12 ± 0.82
	T_{max} , h	4.00 (0.50-16.00)	4.00 (1.00-16.00)	
	AUC_{0-t} , $\mu\text{g}\cdot\text{h/mL}$	68.00 ± 28.51	50.80 ± 19.76	
	$t_{1/2}$, h	10.04 ± 5.86	10.12 ± 6.16	
	K_{el} , 1/h	0.10 ± 0.06	0.10 ± 0.07	
	CL/F , L/h	6.06 ± 4.66	7.59 ± 4.9	
	V/F , L	74.73 ± 52.94	94.71 ± 58.13	
	Fluctuation, %	169.67 ± 53.89	162.86 ± 49.37	
	600 mg	C_{max} , $\mu\text{g/mL}$	8.89 ± 4.23	6.49 ± 2.87
		C_{min} , $\mu\text{g/mL}$	1.50 ± 1.03	1.15 ± 0.78
		C_{avg} , $\mu\text{g/mL}$	4.46 ± 2.18	3.33 ± 1.54
T_{max} , h		4.00 (0.50-12.00)	4.00 (1.00-12.00)	
AUC_{0-t} , $\mu\text{g}\cdot\text{h/mL}$		106.96 ± 52.20	79.97 ± 36.91	
$t_{1/2}$, h		9.46 ± 5.63	9.68 ± 5.98	
K_{el} , 1/h		0.10 ± 0.07	0.10 ± 0.10	
CL/F , L/h		6.60 ± 5.66	8.11 ± 5.95	
V/F , L		72.33 ± 51.95	91.64 ± 57.91	
Fluctuation, %		176.15 ± 55.20	169.68 ± 51.65	

AUC_{0-t} , area under the concentration-time curve between 0 and 24 hours postdose; C_{avg} , average concentration; CL, clearance; C_{max} , maximum concentration; C_{min} , minimum concentration; F, bioavailability; h, hour; K_{el} , elimination rate constant; L, liter; $t_{1/2}$, elimination half-life; T_{max} , time of maximum concentration; V, volume of distribution.

Values are reported as mean \pm standard deviation, except T_{max} , which is median (range). Body weight was included as a covariate (children, 31.5 kg; adolescents, 57.25 kg). Fluctuation is defined as $100 \times (C_{max} - C_{min})/C_{avg}$.

increased proportionally with viloxazine ER doses suggesting linear pharmacokinetics.

Drug Holiday

Thirty-two simulation scenarios were evaluated: 4 doses (100, 200, 400, and 600 mg), 2 age groups (children and adolescents), and up to 4-day periods of missed doses (ie, 1, 2, 3, and 4 holiday days). In each scenario, the median and the 90% prediction interval of the viloxazine levels were computed. For brevity, only the

plots of the median viloxazine exposure at the dose of 400 mg/day in children after 1, 2, 3, and 4 days of drug holiday are presented in Figure 5. The median viloxazine C_{avg} and C_{min} values at steady state, during drug holiday, and during the 3 days after restarting the treatment are presented in Table S2 and Table S3 in the supplemental material.

The simulation results showed that during the off-drug holiday period, viloxazine concentration rapidly declined from the steady-state levels. At all 4 doses, C_{min}

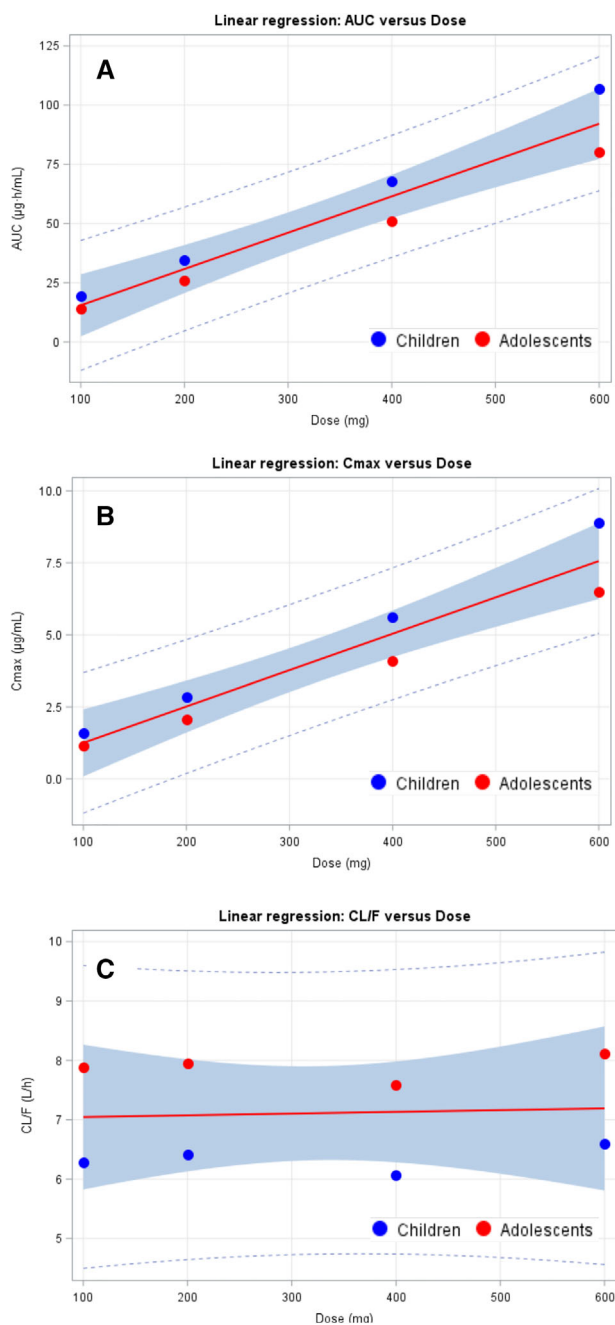


Figure 4. Dose linearity of viloxazine PK parameters. Linear regression of viloxazine ER dose with viloxazine area under the curve (A), maximal concentration (B), and clearance (C). Blue-shaded area represents the 95% confidence interval of the estimated regression line, and the dashed lines delimit the 95% prediction interval.

dropped below the limit of quantification (estimated at $0.01 \mu\text{g/mL}$) after 3 days of drug holiday. Importantly, when daily viloxazine ER dosing was resumed, viloxazine plasma concentrations reached nominal steady-state levels after approximately 2 days of once-a-day dosing, regardless of the dose level or duration of the holiday.

Discussion

Overview

Based on data from 495 pediatric subjects with ADHD, the present analysis describes the population PK model characterizing the PK of viloxazine and its major metabolite 5-HVLX-gluc, identifies significant covariates, and describes the PK consequences of missed viloxazine ER doses. Specifically, these results identify body weight as a potential source of variability among children and adolescents, where greater body weight was associated with decreased drug exposure. Simulations based on these data further determined that, after missed doses of viloxazine ER, plasma concentrations of viloxazine quickly returned to steady-state levels, even after up to 4 days without dosing.

The plasma concentrations of viloxazine and its major metabolite, 5-HVLX-gluc, were well described by a 1-compartment model with first-order absorption and elimination of the parent drug and first-order formation and elimination of the metabolite, as indicated by goodness-of-fit plots, VPCs, and bootstrap analysis. The population PK model, based on a nonlinear mixed-effects modeling approach, indicated that the PK of viloxazine is linear and dose-proportional (Table 3, Figure 4). This is consistent with unpublished data from an early phase 1 study demonstrating linearity and dose proportionality at doses of 300-2100 mg viloxazine ER in healthy adults (data on file), as well as an older study using both oral and intravenous administration of an instant-release viloxazine formulation (200 mg).²⁵

Body Weight

Although the apparent volume of distribution and clearance of viloxazine were related to age because of the significant correlation between age and weight, the effect of age was not significant after controlling for body weight. Therefore, the effect of age on viloxazine PK could be considered negligible relative to that of body weight. These data suggest that, to achieve comparable systemic exposure, heavier patients might require larger doses than patients of lighter body weight. Because weight in pediatric populations tends to be highly correlated with age, as a general rule, older patients might require larger doses than younger patients to achieve comparable C_{max} and AUC.

This inverse relationship between body weight and viloxazine exposure—with exposure decreasing as body weight increases for a given dose strength—is common among a variety of drug classes. Across the 4 pivotal phase 3 studies of viloxazine ER used in the present analysis, children were treated with doses of 100-400 mg/day and adolescents received 200-600 mg/day.²⁻⁵

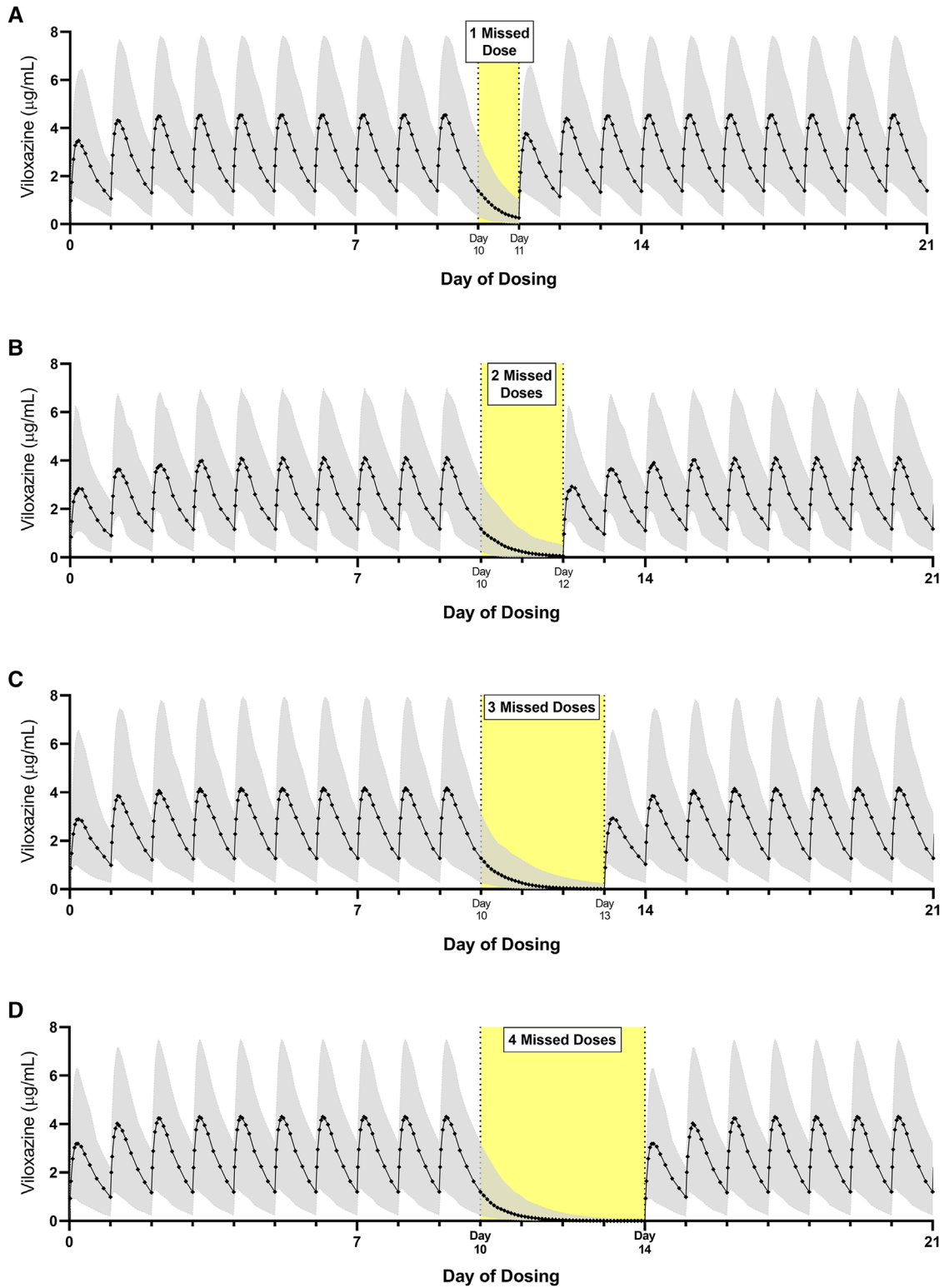


Figure 5. Predicted impact of drug holidays on viloxazine concentrations. Simulated viloxazine concentrations in children treated with 400 mg/day viloxazine extended release after 1, 2, 3, or 4 missed doses (A-D, respectively). The median predicted values are represented by black diamonds and connected by the black lines, and the shaded light-gray area represents the 90% prediction interval. The yellow-shaded area within the dotted vertical lines represents the days of drug holiday.

Notably, statistically significant therapeutic effects were observed at each dose of 100-400 mg/day, with no clear evidence of dose-dependent increases in safety or tolerability issues. These data suggest that viloxazine ER has a wide therapeutic window within which it is likely to be both effective and safe, such that dosing by weight on a milligram per kilogram basis is not necessary.

Drug Holidays

Additional simulations were conducted to estimate the impact of 1, 2, 3, or 4 missed daily doses of viloxazine ER on viloxazine exposure once steady state was achieved. When off drug, viloxazine concentrations rapidly declined from steady-state levels, reaching a value below the limit of quantification (0.01 $\mu\text{g/mL}$) after 3 days of drug holiday, regardless of the dose. However, as soon as daily administration of viloxazine ER was resumed after the off-drug holiday period, viloxazine plasma concentration rapidly reached steady-state concentrations (on average after approximately 2 doses) at all dose levels, regardless of the duration of the interruption.

Although forgetfulness is the most common cause of medication nonadherence, deliberate medication interruptions, particularly from psychostimulants, are sometimes initiated by parents and/or clinicians and are frequently timed with nonschool days such as weekends or school holidays.²⁶⁻²⁸ These predefined drug holidays are usually conducted to fulfill a clinical purpose, such as to combat side effects such as weight loss, slowed growth, or sleep disturbances, minimize the effects of medication tolerance, or reassess the need for medication.^{27,28} For short drug holidays, such as those over a weekend, it is crucial that systemic exposure return to therapeutic levels quickly to provide appropriate symptom control when returning to the classroom Monday morning.

Although patient medication adherence can be increased by various methods (eg, once-daily versus twice-daily dosing, setting reminders), the consequences of missing an occasional dose depends on an individual drug's "forgiveness," or how many doses can be missed while maintaining a therapeutic effect.^{29,30} Drugs with greater forgiveness can blunt the effects of missed or late doses, thereby minimizing potential downstream consequences for efficacy or safety.^{29,30} Although the pharmacodynamic consequences of missed viloxazine ER doses have not been clinically examined, the present analysis suggests plasma concentrations on average are likely to return to steady state within 2 days of resuming once-daily treatment. Because viloxazine ER has been shown to be effective in reducing ADHD symptoms in as little as 1 week,²⁻⁴ any changes in

therapeutic benefits after 1-4 missed doses are likely to normalize quickly upon resuming medication.

Conclusions

Here, a comprehensive PK model was developed to describe the PK profile of viloxazine and its major metabolite, 5-HVLX-gluc, in pediatric individuals with ADHD and to identify potential sources of variability. The model suggests that at the same dose strength, children and adolescents with higher body weight will have lower systemic viloxazine exposure, whereas those with lower body weights will have higher drug exposure. Given viloxazine ER's wide therapeutic window within which it is likely to be both effective and safe (thereby precluding a general need for strict milligram-per-kilogram-based dosing), clinicians should consider the individual needs of their patients and adjust dosage according to the viloxazine ER prescribing information. The model also demonstrated that, after short (1- to 4-day) drug holidays, viloxazine concentrations generally return to steady-state levels quickly. This suggests that the occasional missed or forgotten dose is unlikely to have significant clinical impact on systemic exposure, thereby minimizing the likelihood of subsequent changes to viloxazine ER's therapeutic or safety profile. Population PK analyses such as those reported here can help clinicians to understand which factors are likely to influence a medication's efficacy or safety for their patients and may provide guidance when making treatment decisions.

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Conflicts of Interest

A. Nasser, Z. Wang, A. Kosheleff, L. Xie, and L. Adejo are employees of Supernus Pharmaceuticals, Inc. S. Schwabe was an employee of Supernus Pharmaceuticals, Inc. at the time of this work. R. Gomeni was a paid consultant to Ironshore Pharmaceuticals, Sunovion Pharmaceuticals, Supernus Pharmaceuticals, Teva, Biomedical Science Institutes, Nanomi BVs, Laboratorios Liconsa, Massachusetts General Hospital, UCB, Recordati Rare Diseases, Indivior, Tris Pharma, and F. Hoffmann-La Roche.

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Data Sharing

The data are not available in a repository, but requests can be directed to anasser@supernus.com.

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Supplemental Information

Additional supplemental information can be found by clicking the Supplements link in the PDF toolbar or the Supplemental Information section at the end of web-based version of this article.