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ARTICLE

Estimation of an Appropriate Dose of Trazodone for Pediatric Insomnia and the Potential for a Trazodone–Atomoxetine Interaction

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There is a paucity of clinical trials for the treatment of pediatric insomnia. This study was designed to predict the doses of trazodone to guide dosing in a clinical trial for pediatric insomnia using physiologically-based pharmacokinetic (PBPK) modeling. Data on the pharmacokinetics of trazodone in children are currently lacking. The interaction potential between trazodone and atomoxetine was also predicted. Doses predicted in the following age groups, with exposures corresponding to adult dosages of 30, 75, and 150 mg once a day (q.d.), respectively, were: (i) 2- to 6-year-old group, doses of 0.35, 0.8, and 1.6 mg/kg q.d.; (ii) >6- to 12-year-old group, doses of 0.4, 1.0, and 1.9 mg/kg q.d.; (iii) >12- to 17-year-old group, doses of 0.4, 1.1, and 2.1 mg/kg q.d. An interaction between trazodone and atomoxetine was predicted to be unlikely. Clinical trials based on the aforementioned predicted dosing are currently in progress, and pharmacokinetic data obtained will enable further refinement of the PBPK models.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON TOPIC?

☑ Pediatric insomnia is a common comorbidity in neurodevelopmental disorders (NDDs). Although trazodone is frequently used for its ability to induce and maintain sleep in adults with depressive disorders, equivalent doses for children have not been defined.

WHAT QUESTION DID THIS STUDY ADDRESS?

☑ This study aimed to predict the doses of trazodone to guide dosing in a clinical trial on pediatric insomnia in NDD. In addition, the interaction potential between trazodone and atomoxetine (frequently used in the treatment of attention deficit hyperactivity disorders) was predicted.

HOW DOES THIS STUDY ADD TO OUR KNOWLEDGE?

☑ Pediatric doses of trazodone were predicted from commonly prescribed adult doses used in insomnia using a physiologically-based pharmacokinetic strategy.

HOW MIGHT THIS CHANGE DRUG DISCOVERY, DEVELOPMENT, AND/OR THERAPEUTICS?

☑ Currently there are no approved drugs for the treatment of pediatric insomnia in NDD. These predicted doses of trazodone were used to guide dosing in a pediatric investigational plan to address this need. Prediction of the lack of a potential drug–drug interaction between trazodone and atomoxetine suggests that these two drugs can be coadministered.

Insomnia is a common sleep disorder in children with neurodevelopmental disorders (NDDs) such as autism spectrum disorder, attention deficit hyperactivity disorder (ADHD), Down syndrome, and Rett Syndrome.[1–4] Managing sleep disorders in children is critical both for the child and for the family, and it is often frustrating because of the refractory nature of the problem.[5] In children with NDDs, behavioral techniques for sleep induction may not be successful, thus requiring pharmacological interventions.[1,6] However, because of the paucity of controlled clinical trials, medications for the treatment of pediatric insomnia in children with NDDs still represent an unmet medical need.

Trazodone exerts its antidepressant activity acting as serotonin antagonist and reuptake inhibitor. It is indicated primarily for the treatment of depression in patients who do not respond to antidepressants, such as selective serotonin reuptake inhibitors.[7] As a result of the combined serotoninergic receptor antagonism and serotonin reuptake inhibition, trazodone has demonstrated unique therapeutic flexibility, which has given rise to its potential use in a broad range of comorbidities of major depressive disorder as well as off-label indications, including insomnia.[8,9] Trazodone also shows a sedating activity, with reviews indicating that insomnia is the most common reason for its off-label prescription and use in adult and pediatric populations.[8,10] The hypnotic

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effect of trazodone is promptly achieved, with possible beneficial effects on sleep architecture and quality in depressed patients.[10] Despite favorable anecdotal reports on the use of trazodone in pediatric insomnia, controlled clinical trials to evaluate its efficacy and safety and appropriate dosages in children are lacking. Currently, there are no clinical data on the pharmacokinetics (PK) or efficacy of trazodone in children, thus presenting challenges for the design of prospective clinical trials to evaluate the efficacy of this drug in children. The reliable prediction of relevant pediatric doses from known doses in adults is essential to support the conduct of prospective clinical trials in children.

Although the clinical PK of trazodone has been extensively studied in adults,[11–13] details relevant to the metabolism of trazodone remain unclear. *In vitro* studies have shown that it is metabolized predominantly by cytochrome P450 (CYP)3A4 and CYP3A5 to the active metabolite m-chlorophenylpiperazine (mCPP),[14] (A. Tolonen, unpublished data) with CYP2C19 and CYP2D6 contributing as well to trazodone metabolism into other (inactive) metabolites. Nevertheless, the fraction of the drug *in vivo* metabolized by CYP3A4 (fm_{CYP3A4}) has not been quantified. Results from a study following the intravenous administration of 25 mg ^{14}C-trazodone in healthy volunteers suggested that mCPP formation accounts for at least 35% of trazodone dose.[15] However, once mCPP is formed, it undergoes extensive metabolism,[16] with clinical evidence confirming that the systemic exposure to mCPP in humans accounts for less than 5% of that of trazodone, on a molar basis, (R. Picollo, unpublished data) suggesting a minimal contribution by the metabolite to the pharmacological effect of the drug.

The aim of this study was to develop a physiologically-based PK (PBPK) model for trazodone to estimate an appropriate starting dose for a phase II clinical study designed to evaluate the use of trazodone in the treatment of insomnia in children with ADHD. To our knowledge, this clinical study will be the first study with trazodone in children. In addition, the PK interaction potential between trazodone and atomoxetine (a drug commonly used to treat ADHD) would be predicted.

METHODS

Clinical studies were conducted in compliance with the Declaration of Helsinki and the International Conference on Harmonisation guidelines for Good Clinical Practice. Study protocols and informed consent documents were reviewed and approved by the relevant institutional review boards of the investigational centers. All study patients provided written informed consent.

PBPK modeling strategy

The Simcyp Population-Based Simulator (version 14, release 1; Simcyp Ltd, Sheffield, UK (**Supplementary Information S4**) was used for all simulations. The Simcyp Caucasian Healthy Volunteer population model was used for the adult simulations, whereas the Simcyp Pediatric population model was used for the simulations in children aged 2–6 years, >6–12 years, and >12–17 years. A PBPK model for trazodone was developed using *in vitro* and clinical data. The strategy adopted for modeling and simulations for predicting pediatric doses is summarized in **Figure 1**.

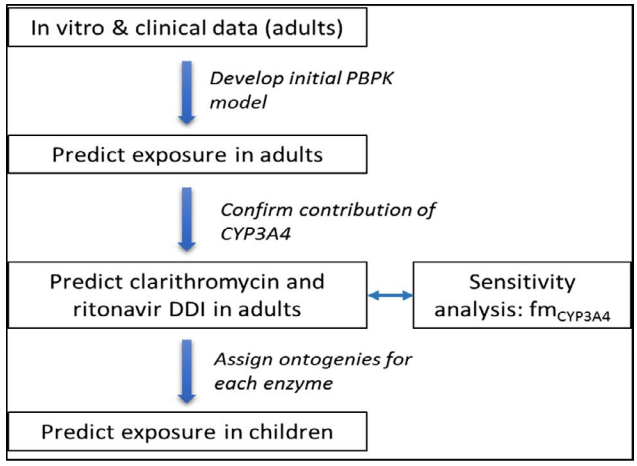

Figure 1 Summary of physiologically-based pharmacokinetic (PBPK) strategy for predicting the exposure of trazodone in children. CYP, cytochrome P450; DDI, drug–drug interaction; $fm_{CYP3A4,}$ CYP3A4 contribution.

Development of trazodone PBPK models

A PBPK model for trazodone was developed based on available physicochemical parameters, data from *in vitro* experiments, clinical PK parameters, and predicted parameters. Derivation of key parameters is described in the next sections. The final parameters used in the model are shown in **Table 1**.

Estimation of CYP3A4-mediated metabolism for trazodone

Details of trazodone metabolic pathway are still lacking, although available evidence suggests that CYP3A4 is predominantly involved. In the absence of an accurate estimate of fm_{CYP3A4}, 100% was initially assumed. Initial simulations using the measured *in vitro* clearance of the unbound drug ($CL_{int,u}$ = 0.37 µL/min/pmol CYP3A4)[17] predicted a clearance of intravenously administered trazodone of 5.72 L/hour and an oral clearance of 7.47 L/hour compared with the observed values of 10 and 13 L/hour, respectively.[18] To fully recover the observed clearances, input parameters for CL_{int} were back calculated from the observed clearance of intravenously administered trazodone using the well-stirred liver model (Eqs. 1 and 2). The CL_{int} was then divided by average population values for liver weight (1,648 g),[19]; mg protein/gram of liver (-39.8 mg protein/g liver)[20] and hepatic CYP enzyme abundance (137 pmol/mg for CYP3A4)[19] to give the CL_{int} in units of µL/min/pmol P450.

$$CLu_{H,int} = \frac{Q_H \times CL_{metH}}{fu_B \left(Q_H - CL_{metH}\right)} \quad (1)$$

$$CL_{metH} = CL_{IV} - CL_R \quad (2)$$

where fu_B is the fraction of unbound drug in blood (calculated from fraction of unbound drug in the plasma divided by the blood to plasma ratio – fu_p/B:P); Q_H is the blood flow in the hepatic vein (90 L/hour); CL_R is the renal clearance (0 L/hour), and CL_{metH} is the hepatic metabolic clearance. A $CL_{int\ CYP3A4}$ of 0.438 µL/min/pmol was used in the model.

Table 1 Input parameter values used to simulate the PK of trazodone

Parameter name	Value	Method/source
Physical chemistry and blood binding		
MW (g/mol)	408.32	[35]
Log P	2.87	Calculated from experimental value of logD 7.4 (=2.79)[36]
Compound type	Monoprotic base	[36]
pK_a	6.61	Measured[36]
B/P	0.68	Calculated from measured E:P ratio of 0.2 (J. Tang, unpublished data).
fu_p	0.0354	Measured by equilibrium dialysis (E. Cozzi, unpublished data).
Model	Full-PBPK	
V_{ss} (L/kg)	1.0	Predicted (Method 2)[37]
Absorption		
F_a	0.98	Predicted from mean P_{app} ($24.2*10^{-6}$ cm/s) obtained in Caco-2 cells and calibrated using metoprolol data ($28.1*10^{-6}$ cm/s)[17]
k_a ($hour^{-1}$)	IR/oral solution: 1.60 ER: 0.07	IR: Predicted from mean P_{app} ($24.2*10^{-6}$ cm/s) obtained in Caco-2 cells and calibrated using metoprolol data ($28.1*10^{-6}$ cm/s)[17] ER: fitting of concentration-time data following a single oral dose of 300 mg ER trazodone[23]
fu_{gut}	1.0	Default value
Elimination		
$CL_{int,CYP3A4}$ (µL/min/pmol)	0.438	Retrograde calculation-assign 70% of hepatic metabolism to CYP3A4 (see Methods section)
Additional HLM CL_{int} (µL/min/mg)	25.7	Retrograde calculation-assign 30% of hepatic metabolism to undefined pathways (see Methods section)

B/P, blood to plasma; CL_{int}, intrinsic clearance; CYP, cytochrome P450; E:P, erythrocyte to plasma ratio; ER, extended release; F_a, fraction absorbed; fu_{gut}, fraction unbound in the gut; fu_p, fraction unbound in plasma; HLM, human liver microsome; IR, immediate release; k_a, absorption rate constant; MW, molecular weight; P_{app}, apparent permeability; PBPK, physiologically-based pharmacokinetic; V_{ss}, volume of distribution.

Trazodone fm_{CYP3A4} was subsequently refined by assessing the inhibition effect of clarithromycin treatment on trazodone systemic exposures and comparing it to those observed in the clinical study.[21] This optimized fm_{CYP3A4} was further verified by assessing the inhibition effect of ritonavir treatment on trazodone systemic exposures.[22] Consequently, trazodone fm_{CYP3A4} was set to 70% in the final model. The balance of the metabolism (30%) was assigned as undefined human liver microsome metabolism in the PBPK model.

Estimation of trazodone absorption parameters

Trazodone oral solution and immediate release (IR) tablets were shown to be bioequivalent (A. Rusca, *et al.*, unpublished data). Based on those findings, the first-order absorption model for the IR model was also used to describe the absorption kinetics of trazodone oral solution. *In vitro* data on the permeability of trazodone were used to predict the fraction absorbed (F_a) for the IR tablets (see **Table 1**) based on Eq. 3.

$$F_a = 1 - (1 + 0.54P_{eff,man})^{-7} \quad (3)$$

The F_a was predicted to be 0.98, compared with the 0.72–0.91 that was previously reported.[18] A first-order absorption model was used to describe the absorption kinetics of trazodone extended release (ER) formulation. The absorption rate constant (k_a) was estimated from clinical data following a single oral dose of 300 mg ER[23] using the weighted least square algorithm and Nelder-Mead method. The initial estimate of k_a was 0.1 $hour^{-1}$ with a range of 0.01–2 $hour^{-1}$. The final k_a estimate was 0.07 $hour^{-1}$.

Simulations for trazodone model development and verification in adults

To verify the developed trazodone model, simulated plasma concentrations were compared with observed clinical data for the following:

- A single oral dose of 50 mg IR or 30, 60, or 90 mg oral solution (A. Rusca, *et al.*, unpublished data)
- Multiple oral doses of 100 mg IR three times daily for 7 days[24]

CYP3A4 contribution (fm_{CYP3A4} = 100%) to the model was assessed by comparing the simulated drug–drug interaction (DDI) between a single 50 mg oral dose (IR) of trazodone (given on day 2) and clarithromycin (500 mg given at 24, 8, and 1 hour prior to and again at 8 hours after administration of trazodone to adult healthy volunteers) with clinical data (M. Zucconi, L. Olivieri and P. Dionisio, unpublished data). The Simcyp default model for clarithromycin was used for these simulations, and the performance of this model in recovering the observed CYP3A4 interaction has been verified by Ke *et al.*[25] The fm_{CYP3A4} value of 100% resulted in an overestimation of the DDI (see the Results section). Sensitivity analysis was used to optimise the fm_{CYP3A4}, resulting in a value of 70%. This refined trazodone model with fm_{CYP3A4} = 70% was further verified by simulating the DDI between a single 50 mg oral dose of trazodone (IR formulation that was administered on day 2) and ritonavir (200 mg twice a day (b.i.d.)) and comparing the PK to clinical data.[22] The Simcyp model for ritonavir (V15 release) was used for these simulations. Verification of the

ritonavir model in recovering the observed CYP3A4 interaction is shown in **Supplementary Information S5**.

Study designs for all of the aforementioned simulations matched the corresponding clinical studies (**Supplementary Information S1**).

Trazodone model refinement for dose estimations in children

Trazodone oral solution was the favored dosage form for the pediatric clinical study. Therefore, the final adult trazodone IR/oral solution model was used for the pediatric dose simulations using the age bands of 2–6 years, >6–12 years, and >12–17 years. Ten-by-ten trials of pediatric subjects (proportion of female = 0.5) in the respective age bands were generated. The prediction of dosage adjustment in children was based on matching the equivalent steady-state exposures (maximum plasma concentration (C_{max})) in adults following 30, 75–150 mg IR trazodone per day. Sensitivity analysis was used to determine the dose for each age band that resulted in a C_{max} similar to that in adults, corresponding to the 30, 75, and 150 mg doses. For the treatment of sleeping disorders, the tested doses ranged from 30–90 mg/day (M. Zucconi, L. Olivieri and P. Dionisio, unpublished data). Therefore, 30 mg was selected to represent the lowest dose levels, and 75 mg was selected to represent an intermediate dosage between 60 and 90 mg. The approved doses for trazodone IR formulation in treating adult major depressive disorder is 150–400 mg/day, with an initial dose of 150 mg.[18]

It was assumed that the F_a and k_a of trazodone relating to the oral solution are not age dependent. Preliminary simulations using the Simcyp mechanistic absorption module, i.e., the Advanced Dissolution, Absorption and Metabolism (ADAM) model, supported this assumption.[26] The pediatric ADAM module accounts for gastrointestinal physiological changes in the pediatric population, including gastric fluid volumes in fasted and fed states, intestinal surface area, intestinal fluid volumes, gastric emptying time, elevated gastric pH in early neonatal period, and so on. The lowest measured solubility for the hydrochloride salt of trazodone of 2.57 mg/mL was used as the intrinsic solubility input, with other formulation-specific parameters set to default Simcyp values for "solution with precipitation" formulation as a result of trazodone sparing solubility. Simulations supported an F_a = 1.0. The systemic exposure of trazodone using the pediatric ADAM model was comparable to that simulated using the first-order absorption model. Further details are shown in **Supplementary Information S2**. Ongoing research will explore the ADAM model further.

In the absence of experimental data, the main plasma binding protein for trazodone was assumed to be albumin. The maturation pattern for albumin (HSA) and for α_1-acid glycoprotein (AAG) are comparable in pediatric patients >2 years old.[27] Thus, the age effect on plasma protein binding of trazodone to either HSA or AAG is expected to be similar. The Simcyp CYP3A enzyme ontogeny was applied to the model, where 70% of trazodone metabolism was assigned to CYP3A4. Of the metabolism, 30% was assigned to undefined human liver microsome metabolism, and an ontogeny function was not applied.

Simulations to predict trazodone doses in children

A thorough QT/QTc study in adults confirmed the moderate effects of trazodone on the QT interval (distance between the Q and T waves on the electrocardiogram) and showed a weak correlation between QTc (QT corrected for heart rate) changes and maximum trazodone concentrations (A. Rusca, *et al.*, unpublished data). The pediatric dose projection in the 2–6, >6–12, and >12–17 age groups primarily focused on matching the equivalent steady-state C_{max} in adults so as to minimize the potential risks of QT/QTc changes in the pediatric population. To reach this aim, the dose in pediatric subjects giving equivalent C_{max} in adults were estimated using sensitivity analysis. The final simulated PK parameters and profiles following adult doses (IR formulation) of 30, 75, and 150 mg once a day (q.d.) were used.

The division of the pediatric population into the 2–6, >6–12, and >12–17 age groups was based on advice from the regulatory authority during discussions of the proposed clinical trial.

Atomoxetine model development

The development of a fit-for-purpose model for atomoxetine focused on the recovery of the clinically observed atomoxetine multiple-dose PK in CYP2D6 extensive metabolizers (EM) and poor metabolizers (PM) because the objective for model application was to assess drug interactions with trazodone as a victim drug.

Reported oral clearance values (estimated using population PK analysis) in CYP2D6 EMs and PMs[28] were used as clearance inputs. Initial simulations using the population PK analysis model estimated a volume of distribution (V_{ss}) of 0.85 L/kg, leading to an underestimation of atomoxetine C_{max} in both EMs and PMs. Thus, the V_{ss} was further optimized (V_{ss} = 0.71 L/kg) based on the fitting of concentration-time profiles following the administration of 20 mg b.i.d. atomoxetine in CYP2D6 PMs.[29]

The *in vitro* measured CYP3A4 concentration of trazodone required to produce half the maximum inhibition of CYP3A4 (K_i)[30] was verified by assessing the inhibition effect of atomoxetine treatment on midazolam (a CYP3A4 substrate) systemic exposure and comparing the predicted exposures with those clinically observed.

All input parameters used in the atomoxetine final model are presented in **Table 2**.

Verification of atomoxetine model and application to DDI

The fit-for-purpose model for atomoxetine was verified by comparing the simulated profiles of atomoxetine 20 or 40 mg following b.i.d. administration in healthy CYP2D6 EMs and PMs with the observed clinical data.[28,29]

A sensitivity analysis was performed to verify the *in vitro* measured CYP3A4 K_i[30] and the fraction of drug unbound in microsomes for atomoxetine using midazolam as a substrate. Details of the study designs and results of atomoxetine model verification are shown in **Supplementary Information S3**.

The verified atomoxetine model was then applied to prospectively predict the interaction between trazodone and atomoxetine. A total of 10 virtual trials of 10 subjects each (aged 20–50 years, proportion of female = 0.5) were generated.

Table 2 Input parameter values used to simulate the PK of atomoxetine

Parameter name	Value	Method/source
Physical chemistry and blood binding		
MW (g/mol)	291.82	[28]
Log P	3.81	Predicted by Chemaxon
Compound type	Monoprotic base	
pK_a	9.8	Predicted by Chemaxon
B/P	0.605	Predicted by Simcyp
fu_p	0.02	[28]
Model	Minimal-PBPK	
V_{ss} (L/kg)	0.71	Optimized; observed V_{ss} is 0.85 L/kg
Absorption		
F_a	1	
K_a ($hour^{-1}$)	0.926	Estimated by Pop-PK analysis[28]
fu_{gut}	1.0	Default
Elimination		
CL/F (L/hour)	CYP2D6 EM: 26.4 (CV%: 55.7) CYP2D6 PM: 2.55 (CV%:18)	Estimated by Pop-PK analysis[28]
CYP3A4 inhibition		
K_i (μM)	34	Measured, measured fu_{mic} is not available; predicted fu_{mic} of 0.54 was applied initially and was optimized to 0.23 (see Section 3.8)

B/P, blood to plasma ratio; CL/F, oral clearance; CYP, cytochrome P450; F_a, fraction unbound; fu_{mic}, fraction of drug unbound in microsomes; fu_p, fraction of drug unbound in plasma; K_a, absorption rate constant; K_i, drug concentration required to produce half the maximum inhibition; PBPK, physiologically-based pharmacokinetic; MW, molecular weight; Pop-PK, population pharmacokinetic.

Each subject received a single oral dose of 150 mg trazodone IR on day 10, 2 hours after the morning dose of atomoxetine (60 mg b.i.d. for 12 days). The dose staggering of 2 hours was selected based on matching the simulated time to reach maximum plasma concentration of trazodone (~ 0.5 hours) and atomoxetine (~ 2.5 hours) to maximize the extent of interaction.

Verification of the predictive performance of the PBPK models in this study

Predictive performance of the models were evaluated by the ratios of the predicted:observed PK parameters, such as area under the plasma concentration-time curve (AUC) and C_{max}. Due to the potential variability in the clinical data and the more complex DDI mechanisms involved, model predictions were deemed to be acceptable when they were within 1.5–fold of the observed data.[31] In addition, predicted concentration-time profiles were compared with those observed in clinical studies (visual inspection).

RESULTS

Simulations of trazodone PK for single oral dose as 50 mg IR tablet or 30, 60, or 90 mg oral solution formulation in healthy adults

PK parameters and concentration time profiles of the observed and simulated data for 50 mg IR tablet and 30, 60, or 90 mg oral solution formulation of trazodone in healthy adults are presented in **Table 3** and **Figure 2**. The AUC predicted/AUC observed and C_{max} predicted/C_{max} observed ratios were within 1.5-fold, thus indicating acceptable recovery of the clinical data by the trazodone PBPK model.

Simulations of the PK of 100 mg IR tablet of trazodone given three times a day for 7 days in healthy adults

This simulation resulted in a mean C_{max} of 1,822 ng/mL, compared with the clinically observed mean C_{max} of 3,026 ng/mL. The predicted mean $AUC_{0–24}$ was 24,982 ng × hour/mL compared with a clinically observed value of 32,136 ng × hour/mL. The predicted/observed mean C_{max} and AUC ratios were 0.60 and 0.78, respectively. The observed diurnal variation on trazodone PK following 100 mg IR three times a day (A. Nell, M. Burger, M.T. Rosignoli, R. Picollo and P. Dionisio, unpublished data) was not accounted for in the simulations. The slight underestimation of C_{max} can probably be attributed to the absence of the diurnal variation in the model.

Simulation of trazodone interaction with clarithromycin

To verify trazodone fm_{CYP3A4}, the inhibitory effect of clarithromycin (dosed as 500 mg at 24, 8, and 1 hour prior to and again at 8 hours after administration of trazodone) on CYP3A4 and, consequently, on trazodone (single dose of 50 mg IR on day 2) systemic exposure was assessed. A fm_{CYP3A4} of 100% in the base model led to an overestimation of the DDI. The predicted trazodone AUC and C_{max} ratios were 2.77 and 1.45, respectively, compared with the observed ratios of 1.99 and 1.35, respectively.[21] Because of the uncertainty with the assumption of fm_{CYP3A4} = 100%, a sensitivity analysis of fm_{CYP3A4} was subsequently conducted, and a reduction of trazodone fm_{CYP3A4} to 70% allowed the recovery of the observed clarithromycin DDI data (**Table 3**). The refined model, assuming fm_{CYP3A4} of 70%, generated predicted trazodone AUC and C_{max} ratios of 2.09 and 1.28, respectively, consistent with the observed ratios of 1.99 and 1.35, respectively (**Table 3**).

Simulation of trazodone interaction with ritonavir

Using the refined trazodone model with the optimized $fm_{CYP3A4,}$ trazodone-predicted AUC and C_{max} ratios were 3.14 and 1.39, respectively, compared with the observed ratios of 2.37 and 1.34, respectively (**Table 3**). Because the predicted ratios were within 1.5-fold of the observed ratios, this trazodone model was considered acceptable.

Predicted doses and PK parameters based on matching pediatric and adult C_{max} to relevant adult doses

The final simulated C_{max}, AUC, and concentration-time profiles corresponding to adult doses of 30, 75, and 150 mg IR q.d. are shown in **Table 4** and **Figure 3**.

Predicted doses in the following age groups, based on predicted exposures corresponding to adult dosages of 30, 75, and 150 mg q.d., respectively, were:

- For 2- to 6-year-old group, doses of 0.35, 0.8, and 1.6 mg/kg q.d.

Table 3 Summary results of the verification of the trazodone and atomoxetine models

Trazodone model verification using PK simulations of solutions and IR tablets								
Dose	**50 mg IR**		**30 mg solution**		**60 mg solution**		**90 mg solution**	
Parameter	**C_{max} (ng/mL)**	**AUC_{0-48} (ng/mL hour)**	**C_{max} (ng/mL)**	**AUC_{0-48} (ng/mL hour)**	**C_{max} (ng/mL)**	**AUC_{0-48} (ng/mL hour)**	**C_{max} (ng/mL)**	**AUC_{0-48} (ng/mL hour)**
Predicted mean	619.8	4,660.3	387.9	2,805.3	775.8	5,610.5	1,163.6	8,415.8
Observed mean[25]	692	4,970	446	2,892	807	5,610	1,091	8,811
Predicted: Observed	0.90	0.94	0.87	0.97	0.96	1.0	1.07	0.96

Trazodone model verification using clarithromycin and ritonavir DDIs								
Dose	**50 mg IR trazodone**		**50 mg IR trazodone + 500 mg clarithromycin**		**50 mg IR trazodone**		**50 mg IR trazodone + 200 mg b.i.d. ritonavir**	
Parameter	**C_{max} (ng/mL)**	**AUC (ng/mL h)**	**C_{max} (ng/mL)**	**AUC (ng/mL h)**	**C_{max} (ng/mL)**	**AUC (ng/mL h)**	**C_{max} (ng/mL)**	**AUC (ng/mL h)**
Predicted mean	635	4,470	812	9,529	617	4,455	850	12,958
Observed mean[26]	681	4,668	922	9,275	842	5,860	1,125	13,880
Predicted ratio			1.28	2.09			1.39	3.14
Observed ratio			1.35	1.99			1.34	2.37
Predicted: Observed			0.95	1.05			1.04	1.32

Atomoxetine model verification using PK simulations of 20 mg b.i.d. and 40 mg b.i.d. in CYP2D6 EM and PM								
Dose	**20 mg b.i.d.: EM**		**20 mg b.i.d.: PM**		**40 mg b.i.d.: EM**		**40 mg b.i.d.: EM**	
Parameter	**C_{max} (ng/mL)**	**AUC (ng/mL hour)**	**C_{max} (ng/mL)**	**AUC (ng/mL hour)**	**C_{max} (ng/mL)**	**AUC (ng/mL hour)**	**C_{max} (ng/mL)**	**AUC (ng/mL hour)**
Predicted mean	171	1,180	776	8,210	355	2,025	1,608	16,602
Observed mean	160	1,080	915	8,440	527	2,590	1,949	18,600
Predicted: Observed	1.07	1.09	0.85	0.97	0.67	0.78	0.83	0.89

AUC, area under the plasma concentration-time curve; b.i.d., twice a day; C_{max}, maximum plasma concentration; CYP, cytochrome P450; DDI, drug–drug interaction; EM, extensive metabolizers; IR, immediate release; PK, pharmacokinetic; PM, poor metabolizers.

- For >6- to 12-year-old group, doses of 0.4, 1.0, and 1.9 mg/kg q.d.
- For >12- to 17-year-old group, doses of 0.4, 1.1, and 2.1 mg/kg q.d.

Simulations of 20 mg b.i.d. and 40 mg b.i.d. atomoxetine PK in healthy adults

The mean simulated C_{max} and AUC values for atomoxetine 20 mg b.i.d. were 171 ng/mL and 1,180 ng × hour/mL, respectively, in CYP2D6 EMs and 776 ng/mL and 8,210 ng × hour/mL, respectively, in PMs. The corresponding C_{max} and AUC observed values were 160 ng/mL and 1,080 ng × hour/mL, respectively, in EMs and 915 ng/mL and 8,440 ng × hour/mL, respectively, in PMs.[29] The predicted/observed ratios for C_{max} and AUC were, respectively, 1.07 and 1.09 for EMs and 0.85 and 0.97 for PMs, indicating good recovery of the clinical data.

Mean simulated C_{max} and AUC values for atomoxetine 40 mg b.i.d. were 355 ng/mL and 2,025 ng × hour/mL, respectively, in CYP2D6 EMs and 1,608 ng/mL and 16,602 ng × hour/mL, respectively, in PMs. The corresponding C_{max} and AUC observed values were 527 ng/mL and 2,590 ng × hour/mL, respectively, in EMs and 1,949 ng/mL and 18,600 ng × hour/mL, respectively, in PMs.[28] The predicted/observed ratios for C_{max} and AUC were, respectively, 0.67 and 0.78 for EMs and 0.83 and 0.89 for PMs, indicating acceptable recovery of clinical data, although C_{max} was marginally underpredicted in EMs.

Simulation of the interaction between trazodone and atomoxetine

Estimations of DDI potential indicates that in CYP2D6 PMs, where the DDI magnitude is expected to be the most significant, trazodone AUC and C_{max} predicted ratios were 1.06 and 1.05, respectively. In CYP2D6 EMs, trazodone AUC and C_{max} predicted ratios were 1.01 and 1.01, respectively. These ratios indicate that an interaction between trazodone and atomoxetine is not likely to occur.

DISCUSSION

This PBPK study was designed to predict appropriate pediatric doses of trazodone for its use in a pediatric clinical

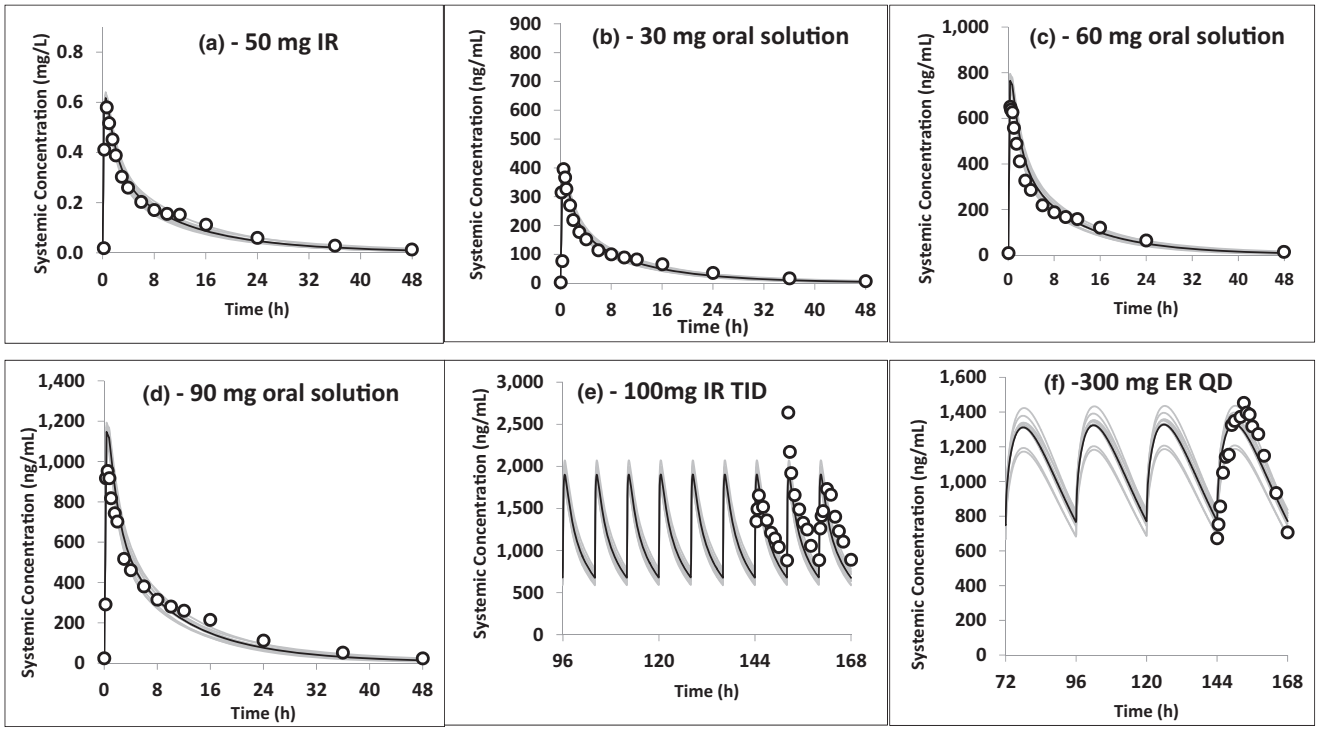

Figure 2 Predicted (black line represents mean, and gray lines represent individual trials) and observed (circles; (**a–d**) 31, (**e**) 32, (**f**) 25, 32) trazodone plasma concentration profiles following the administration of different doses and formulations. ER, extended release; IR, immediate release; q.d., once a day; TID, three times a day.

Table 4 Final predicted pediatric doses corresponding to adult exposure following relevant doses

Age range, y	Median BW in the virtual population, kg	Dose, mg/kg q.d.	$AUC_{0-24\ hours,\ day\ 7}$ (ng/mL × hour), geometric mean (95% CI)	$C_{max,\ day\ 7}$ (ng/mL), geometric mean (95% CI)
Final predicted pediatric doses (q.d.) and PK parameters based on matching the adult trazodone C_{max} following 30 mg IR q.d. for 7 days				
2–6	16	0.35	1,876.2 (1,736.8–2,026.8)	408 (395.2–421.2)
>6–12	28	0.4	2,060 (1,897.5–2,236.4)	400.5 (386.9–414.6)
>12–17	51	0.4	2,178.7 (2,012.5–2,358.6)	376.7 (362.8–391.1)
Adult	73	30 mg	2,619.2 (2,402.7–2,855.3)	416.9 (398.8–435.7)
Final predicted pediatric doses (q.d.) and PK parameters based on matching the adult trazodone C_{max} following 75 mg IR q.d. for 7 days				
2–6	16	0.8	4,304.6 (3,963.3–4,675.3)	945.9 (916.5–976.5)
>6–12	28	1.0	4,954.9 (4,558.4–5,385.8)	991.6 (959.3–1,025.0)
>12–17	51	1.1	5,718.3 (5,238.2–6,242.5)	1,037.5 (998.4–1,078.2)
Adult	73	75 mg	6,369.5 (5,800.3–6,994.7)	1,025.2 (978.9–1,073.6)
Final predicted pediatric doses (q.d.) and PK parameters based on matching the adult trazodone C_{max} following 150 mg IR q.d. for 7 days				
2–6	16	1.6	8,609.3 (7,926.7–9,350.6)	1,891.9 (1,833.0–1,952.7)
>6–12	28	1.9	9,414.3 (8,661.0–10,233.1)	18,84.1 (1,822.6–1,947.6)
>12–17	51	2.1	10,916.8 (10,000.2–11,917.5)	1,980.7 (1,906.0–2,058.4)
Adult	73	150 mg	12,739.1 (11,600.6–13,989.3)	2,050.4 (1,957.9–2,147.3)

$AUC_{0-24\ hours,\ day\ 7}$, area under the plasma concentration-time curve from 0 to 24 hours on day 7; BW, body weight; CI, confidence interval; C_{max}, maximum plasma concentration; IR, immediate release; PK, pharmacokinetic; q.d., once a day.

trial. In the absence of clinical data on PK and efficacy of trazodone in children, this approach was essential for initial dose prediction that enabled ethical and regulatory approval for the clinical trial. Traditional allometric methods of dose prediction in children are frequently inaccurate because they are based on body weight (BW) changes without considering the impact of early childhood maturation in body composition, organ maturation, and ontogeny of eliminating enzymes, which are generally nonlinear with age.[32] Scaling by BW and body surface area or $BW^{0.75}$ were tested for 30

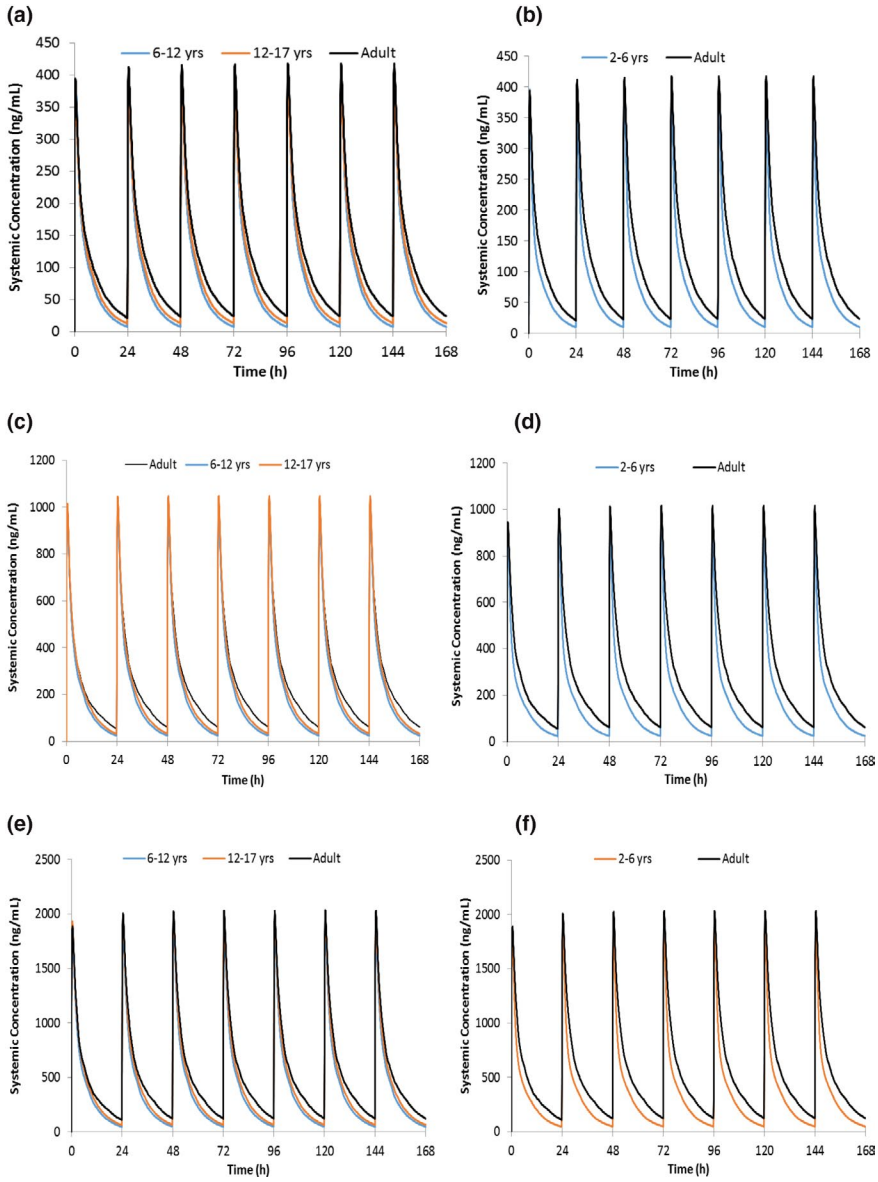

Figure 3 Predicted median total plasma concentration-time profiles of trazodone following the respective predicted final doses in 2–6, >6–12, and > 12–17 year olds. These were based on matching the adult C_{max} following 30 mg IR q.d. for 7 days (**a,b**), 75 mg IR q.d. for 7 days (**c,d**), and 150 mg IR q.d. for 7 days (**e,f**). h, hour; yrs, years.

different drugs. The BW scaling method underpredicted the majority of doses across the pediatric range. The body surface area and $BW^{0.75}$ methods overpredicted some doses by up to 2.86-fold.[33] PBPK modeling was the method approved for dose prediction by the regulatory authority in this case because it has the potential to integrate information from age-specific physiological and biochemical data as well as data from preclinical, clinical, and *in vitro* sources to elucidate PK changes in children and complement pediatric studies and investigational plans.[34]

The pediatric dose projection primarily focused on matching the equivalent steady-state C_{max} in adults to minimize the potential risk of QT/QTc changes. However, corresponding AUCs were also evaluated and shown to be within the corresponding adult ranges. The developed and verified model for trazodone showed acceptable recovery of clinical data in the adult population prior to its application to the pediatric population for dose prediction.

Doses predicted in the following age groups for exposures corresponding to adult dosages of 30, 75, and 150 mg q.d., were:

- 2- to 6-year-old group, doses of 0.35, 0.8, and 1.6 mg/kg q.d., respectively
- >6- to 12-year-old group, doses of 0.4, 1.0, and 1.9 mg/kg q.d., respectively
- >12- to 17-year-old group, doses of 0.4, 1.1, and 2.1 mg/kg q.d., respectively

Based on these predictions, the following dosing strategy was adopted and approved by the regulator for a Pediatric Investigational Plan.

A total of children will be recruited in each of the age groups (2–6, >6–12, and >12–17 years) and stratified by age and dose level as follows:

- Arm 1: 0.25 mg/kg q.d. corresponding to 20 mg q.d. in adults
- Arm 2: 0.4 mg/kg q.d. corresponding to 30 mg q.d. in adults
- Arm 3: 0.5 mg/kg q.d. corresponding to 40 mg q.d. in adults.

The use of the doses predicted using PBPK modeling marked an important milestone toward the prospective testing of trazodone for insomnia in children. Data generated from the clinical trial based on these predicted doses will inform further model refinement in the future. The approach adopted for trazodone can be extended to other drugs where initial dosing in children presents a challenge.

Assumptions and limitations of the models are discussed. First, it is assumed that the pharmacodynamic effects of trazodone are equivalent with similar exposure in adults and children. No information is currently available to support the contrary. Although a key component of the trazodone model was a robust fm_{CYP3A4} parameter, data for a precise estimate of this parameter were unavailable. Based on *in vitro* data and relevant drug-interaction studies, an estimate of 70% was obtained for fm_{CYP3A4}. A mass balance study would be useful in obtaining a more accurate estimate for this parameter. CYP3A4 is the main enzyme contributing to the elimination of trazodone. The ontogeny profile of CYP3A4 showed that the hepatic CYP3A4 activity reached the adult level by the approximate age of 2 years. Therefore, the key factors that drove dose projection in the pediatric populations included age, body mass, liver size, liver blood flow, and plasma protein binding. The main plasma binding protein for trazodone was assumed to be albumin. However, the HSA and AAG are comparable in pediatric patients >2 years old.[27] Thus, the age effect on plasma protein binding of trazodone to either HSA or AAG is expected to be similar. A first-order absorption model was used in all of the pediatric simulations with the same adult k_a and F_a values based on the assumption that k_a and F_a of trazodone oral solution are not age dependent. Preliminary investigations using the ADAM model showed no age-dependent effect on F_a and provided systemic exposure of trazodone comparable to that simulated from the first-order absorption model with the same adult k_a and F_a values.

Simulations of the trazodone interaction with atomoxetine indicated that no potential interaction is expected. Because atomoxetine is frequently used in NDDs, these predictions are reassuring and indicate that trazodone can be used concurrently with atomoxetine.

It can be concluded that the previously predicted doses of trazodone can be used to guide dosing in the initial clinical trials in pediatrics as endorsed by the European Medicines Agency (ref. EMEA-002142-PIP01-17), prior to conducting the first controlled clinical study in pediatrics. The conduct of a clinical trial in pediatrics is now in progress based on the previous dose predictions. Ethical and regulatory approvals for the clinical trial were based on the doses predicted in this analysis. PK data collection was recommended during the clinical trial for further verification of the doses and refinement of the PBPK models.

Supporting Information. Supplementary information accompanies this paper on the *CPT: Pharmacometrics & Systems Pharmacology* website (www.psp-journal.com).

Supplementary Information S1. Study designs used for trazodone model development and verification
Supplementary Information S2. Simulation of trazodone pharmacokinetics in the 2–6 and 6–12 years old using the Paediatric ADAM model
Supplementary Information S3. Atomoxetine model verification and simulations
Supplementary Information S4. Model Code
Supplementary Information S5. References

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Conflict of Interest. L.O., R.P., V.P., F.C., F.G. and S.T. are employees of Angelini S.p.A. A.B.K. and M.C. are employees of Certara UK, Simcyp Division.

Author Contributions. M.C., L.O., R.P., V.P., F.G., F.C., and S.T. wrote the manuscript. A.B.K., L.O., R.P., V.P., F.G., and S.T. designed the research. A.B.K. performed the research and analyzed the data.

1. Souders, M.C. *et al.* Sleep behaviors and sleep quality in children with autism spectrum disorders. *Sleep* **32**, 1566–1578 (2009).
2. Angriman, M., Caravale, B., Novelli, L., Ferri, R. & Bruni, O. Sleep in children with neurodevelopmental disabilities. *Neuropediatrics* **46**, 199–210 (2015).
3. Hvolby, A., Jørgensen, J. & Bilenberg, N. Actigraphic and parental reports of sleep difficulties in children with attention-deficit/hyperactivity disorder. *Arch. Pediatr. Adolesc. Med.* **162**, 323–329 (2008).
4. Miano, S. & Ferri, R. Epidemiology and management of insomnia in children with autistic spectrum disorders. *Paediatr. Drugs* **12**, 75–84 (2010).
5. Blackmer, A.B. & Feinstein, J.A. Management of sleep disorders in children with neurodevelopmental disorders: a review. *Pharmacotherapy* **36**, 84–98 (2016).
6. Pelayo, R. & Yuen, K. Pediatric sleep pharmacology. *Child Adolesc. Psychiatric Clin. North America* **21**, 861–883 (2012).
7. Santarsieri, D. & Schwartz, T.L. Antidepressant efficacy and side effect burden: a quick guide for clinicians. *Drugs Context* **4**, 212290 (2015).
8. Bossini, L., Casolaro, I., Koukouna, D., Cecchini, F. & Fagiolini, A. Off-label uses of trazodone: a review. *Expert Opin. Pharmacother.* **13**, 1707–1717 (2012).
9. Bossini, L. *et al.* Off-label trazodone prescription: evidence, benefits and risks. *Curr. Pharm. Des.* **21**, 3343–3351 (2015).
10. Bruni, O. *et al.* Angriman Practitioner Review: Treatment of chronic insomnia in children and adolescents with neurodevelopmental disabilities. *J. Child Psychol. Psychiat.* **59**, 489–508 (2018).
11. Bayer, A.J., Pathy, M.S. & Ankier, S.I. Pharmacokinetic and pharmacodynamic characteristics of trazodone in the elderly. *Br. J. Clin. Pharmacol.* **16**, 371–376 (1983).
12. Nilsen, O.G. & Dale, O. Single dose pharmacokinetics of trazodone in healthy subjects. *Basic Clin. Pharmacol. Toxicol.* **71**, 150–153 (1992).
13. Nilsen, O.G., Dale, O. & Husebe, B. Pharmacokinetics of trazodone during multiple dosing to psychiatric patients. *Basic Clin. Pharmacol. Toxicol.* **72**, 286–289 (1993).
14. Rotzinger, S., Fang, J. & Baker, G.B. Trazodone is metabolized to m-chlorophenylpiperazine by CYP3A4 from human sources. *Drug Metab. Dispos.* **26**, 572–575 (1998).
15. Jauch, R., Kopitar, Z., Prox, A. & Zimmer, A. Pharmacokinetics and metabolism of trazodone in man. *Arzneimittelforschung* **26**, 2084–2089 (1976).
16. von Moltke, L.L. *et al.* Nefazodone, meta-chlorophenylpiperazine, and their metabolites in vitro: cytochromes mediating transformation, and P450–3A4 inhibitory actions. *Psychopharmacology* **145**, 113–122 (1999).

17. Gertz, M., Harrison, A., Houston, J.B. & Galetin, A. Prediction of human intestinal first-pass metabolism of 25 CYP3A substrates from in vitro clearance and permeability data. *Drug Metab. Dispos.* **38**, 1147–1158 (2010).
18. Greenblatt, D.J. *et al*. Trazodone kinetics: effect of age, gender, and obesity. *Clin. Pharmacol. Ther.* **42**, 193–200 (1987).
19. Barter, Z.E., Tucker, G.T. & Rowland-Yeo, K. Differences in cytochrome p450-mediated pharmacokinetics between Chinese and Caucasian populations predicted by mechanistic physiologically based pharmacokinetic modelling. *Clin. Pharmacokinet.* **52**, 1085–1100 (2013).
20. Barter, Z.E., Chowdry, J.E., Harlow, J.R., Snawder, J.E., Lipscomb, J.C. & Rostami-Hodjegan, A. Covariation of human microsomal protein per gram of liver with age: absence of influence of operator and sample storage may justify inter laboratory data pooling. *Drug Metab. Dispos.* **36**, 2405–2409 (2008).
21. Farkas, D., Volak, L.P., Harmatz, J.S., von Moltke, L.L., Court, M.H. & Greenblatt, D.J. Short-term clarithromycin administration impairs clearance and enhances pharmacodynamic effects of trazodone but not of zolpidem. *Clin. Pharmacol. Ther.* **85**, 644–650 (2009).
22. Greenblatt, D.J. *et al*. Short-term exposure to low-dose ritonavir impairs clearance and enhances adverse effects of trazodone. *J. Clin. Pharmacol.* **43**, 414–422 (2003).
23. Karhu, D., Groenewoud, G., Potgieter, M.A. & Mould, D.R. Dose proportionality of once-daily trazodone extended-release caplets under fasting conditions. *J. Clin. Pharmacol.* **50**, 1438–1449 (2010).
24. Karhu, D., Gossen, E.R., Mostert, A., Cronje, T. & Fradette, C. Safety, tolerability and pharmacokinetics of once-daily trazodone extended-release caplets in healthy subjects. *Int. J. Clin. Pharmacol. Ther.* **49**, 730–743 (2011).
25. Ke, A.B., Zamek-Gliszczynski, M.J., Higgins, J.W. & Hall, S.D. Itraconazole and clarithromycin as ketoconazole alternatives for clinical CYP3A inhibition studies. *Clin. Pharmacol. Ther.* **95**, 473–476 (2014).
26. Patel, N., Polak, S., Jamei, M., Rostami-Hodjegan, A. & Turner, D.B. Quantitative prediction of formulation-specific food effects and their population variability from in vitro data with the physiologically-based ADAM model: a case study using the BCS/BDDCS Class II drug nifedipine. *Eur. J. Pharm. Sci.* **57**, 240–249 (2014).
27. Johnson, T.N., Rostami-Hodjegan, A. & Tucker, G.T. Prediction of the clearance of eleven drugs and associated variability in neonates, infants and children. *Clin. Pharmacokinet.* **45**, 931–956 (2006).
28. US Food and Drug Administration, Centre for Drug Evaluation and Research. Strattera clinical pharmacology and biopharmaceutics review. Study HFBJ <http://www.accessdata.fda.gov/drugsatfda_docs/nda/2002/21-411_Strattera_biopharmr_P2.pdf> (2002).
29. Sauer, J.M. *et al*. Disposition and metabolic fate of atomoxetine hydrochloride: the role of CYP2D6 in human disposition and metabolism. *Drug Metab. Dispos.* **31**, 98–107 (2003).
30. Sauer, J.M. *et al*. Atomoxetine hydrochloride: clinical drug-drug interaction prediction and outcome. *J. Pharmacol. Exp. Ther.* **308**, 410–418 (2004).
31. Wagner, C., Pan, Y., Hsu, V., Sinha, V. & Zhao, P. Predicting the effect of CYP3A inducers on the pharmacokinetics of substrate drugs using physiologically based pharmacokinetic (PBPK) modeling: an analysis of PBPK submissions to the US FDA. *Clin. Pharmacokinet.* **54**, 117–127 (2015).
32. Johnson, T.N., Rostami-Hodjegan, A. & Tucker, G.T. A comparison of methods to predict drug clearance in neonates, infants and children. *Br. J. Clin. Pharmacol.* **57**, 677–678 (2004).
33. Johnson, T.N. Modelling approaches to dose estimation in children. *Br. J. Clin. Pharmacol.* **59**, 663–669 (2005).
34. Maharaj, A.R. & Edginton, A.N. Physiologically based pharmacokinetic modeling and simulation in pediatric drug development. *CPT Pharmacometrics Syst. Pharmacol.* **3**, e148 (2014).
35. Trazodone Investigator's Brochure 8656B01. Version 7.0 (Angelini S.p.A., Pomezia, 2013).
36. Desyrel (trazodone) US prescribing information <https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/018207s032lbl.pdf>.
37. Rodgers, T. & Rowland, M. Mechanistic approaches to volume of distribution predictions: understanding the processes. *Pharm. Res.* **24**, 918–933 (2007).