Estimation of an appropriate dose of trazodone for paediatric insomnia, and the potential for a trazodone-atomoxetine interaction

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Running Title: Estimating a paediatric dose for trazodone

ABSTRACT

There is a paucity of clinical trials for the treatment of paediatric insomnia. This study was designed to predict doses of trazodone to guide dosing in a clinical trial for paediatric insomnia, using physiologically based pharmacokinetic (PBPK) modelling. Data on the pharmacokinetics of trazodone in children is 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 mg, 75 mg and 150 mg once-a-day (QD) respectively were:

2-6 yr old group: doses of 0.35, 0.8 and 1.6 mg/kg QD,

>6-12 yr old group: doses of 0.4, 1.0 and 1.9 mg/kg QD,

>12-17 yr old group: doses of 0.4, 1.1 and 2.1 mg/kg QD.

An interaction between trazodone and atomoxetine was predicted to be unlikely.

Clinical trials based on the above predicted dosing are currently in progress and pharmacokinetic data obtained will enable further refinement of the PBPK models.

INTRODUCTION

Insomnia is a common sleep disorder in children with neurodevelopmental disorders (NDD) such as Autism Spectrum Disorder (ASD), Attention Deficit Hyperactivity Disease (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 due to the refractory nature of the problem **5**. In children with NDD, behavioral techniques for sleep induction may not be successful, thus requiring pharmacological interventions **1,6**. However, due to the paucity of controlled clinical trials, medications for the treatment of paediatric insomnia in children with NDD 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**. Due to 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 co-morbidities 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 paediatric populations **8,10**. The hypnotic 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 paediatric 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 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. Reliable prediction of relevant paediatric doses from known doses in adults is essential to support the conduct of prospective clinical trials in children.

Although the clinical pharmacokinetics (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 CYP3A4 and CYP3A5 to the active metabolite m-chlorophenylpiperazine (mCPP) **14,15**, 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 **16**. However, once mCPP is formed, it undergoes extensive metabolism **17**, 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 **18**, 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 pharmacokinetic (PBPK) model for trazodone to estimate an appropriate starting dose for a Phase 2 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 pharmacokinetic 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 ICH guidelines for Good Clinical Practice. Study protocols and informed consent documents were reviewed and approved by the relevant institutional review boards of the investigational centres. All study patients provided written informed consent.

PBPK modeling strategy

The Simcyp Population-Based Simulator (Version 14 release 1) was used for all the simulations (Simcyp Ltd, Sheffield, United Kingdom). The Simcyp Caucasian Healthy Volunteer population model was used for the adult simulations, while the Simcyp Paediatric 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 modelling and simulations for predicting paediatric doses is summarized in **Fig 1**.

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 below. 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 ($CL_{int,u}$ = 0.37µL/min/pmol CYP3A4) **24**, predicted a clearance of intravenously administered trazodone (CL_{IV}) of 5.72 L/h and an oral clearance (CL_{PO}) of 7.47 L/h, compared with the observed values of 10 L/h and 13 L/h respectively **26**. In order to fully recover the observed clearances, input parameters for CL_{int} were back-calculated from the observed CL_{IV} using the well-stirred liver model (Equation 1 and Equation 2). The CL_{int} was then divided by average population values for

liver weight (1648 g) **27**, mg protein/gram of liver - MPPGL (39.8 mg protein/g liver) **28** and hepatic CYP enzyme abundance (137 pmol/mg for CYP3A4) **27** to give the CL_{int} in units of µl/min/pmol P450.

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

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

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/hr); CL_R is the renal clearance (0 L/hr) and CL_{metH} is the hepatic metabolic clearance. A $CL_{int\ CYP3A4}$ of 0.438 µL/min/pmol was used in the model.

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 **29**. This optimized fm_{CYP3A4} was further verified by assessing the inhibition effect of ritonavir treatment on trazodone systemic exposures **30**. 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 (HLM) metabolism in the PBPK model.

Estimation of trazodone absorption parameters

Trazodone oral solution and immediate release (IR) tablets were shown to be bioequivalent **31**. 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 (Fa) for the IR tablets (see **Table 1**), based on equation 3.

$$\mathbf{Fa = 1 - (1 + 0.54\ P_{eff,man})^{-7}} \quad \text{Equation (3)}$$

The Fa was predicted to be 0.98, compared with the 0.72 to 0.91 that was previously reported **26**. A first-order absorption model was used to describe the absorption kinetics of trazodone extended release (ER) formulation. The k_a was estimated from clinical data following a single oral dose of 300 mg ER **25**, using the Weighted Least Square algorithm and Nelder-Mead method.

The initial estimate of k_a was 0.1 hr^{-1} with a range of 0.01 to 2 hr^{-1}. The final k_a estimate was 0.07 hr^{-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:

* a single oral dose of 50 mg IR or 30, 60 or 90 mg oral solution **31**;

*multiple oral doses of 100 mg IR three times daily for 7 days **32**.

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 h, 8 h and 1 h prior to and again at 8 h after administration of trazodone, to adult healthy volunteers) with clinical data **29.** 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 and coworkers **33.** The fm_{CYP3A4} value of 100% resulted in an over estimation of the DDI (see 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 BID) and comparing the PK to clinical data **30**. 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 the Supplementary Information (S5).

Study designs for all the above simulations matched the corresponding clinical studies (S1).

Trazodone model refinement for dose estimations in children

Trazodone oral solution was the favored dosage form for the paediatric clinical study. Therefore, the final adult trazodone IR/oral solution model was used for the paediatric dose simulations using the age bands of 2 to 6 years, > 6 to 12 years and > 12 to 17 years. Ten by ten trials of paediatric 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 (C_{max}) in adults following 30, 75 mg to 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 disorder, the tested doses ranged from 30 to 90 mg/day **34**. 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 to 400 mg/day, with an initial dose of 150 mg **20**.

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 & Metabolism (ADAM) model, supported this assumption **35**. The paediatric ADAM module accounts for gastro-intestinal (GI) physiological changes in the paediatric 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, etc. The lowest measured solubility for trazodone-HCL 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, due to trazodone sparing solubility. Simulations supported an F_a = 1.0. The systemic exposure of trazodone using the paediatric ADAM model was comparable to that simulated using the first order absorption model. Further details are shown in the 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 paediatrics > 2 years old **36**. 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. Thirty percent of the metabolism was assigned to undefined HLM 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 and showed a weak correlation between QTc changes and maximum trazodone concentrations **37**. The paediatric dose projection in the 2-6 yr, >6-12 yr and >12-17yr 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 paediatric population. To reach this aim, the dose in paediatric 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 mg QD, 75 mg QD and 150 mg QD were utilized.

The division of the paediatric population into the 2-6 yr, >6-12 yr and >12-17yr 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), since the objective for model application was to assess drug interactions with trazodone as a victim drug.

Reported CL/F values (estimated using population pharmacokinetic analysis (Pop-PK) in CYP2D6 EMs and PMs **38** were used as clearance inputs. Initial simulations using the Pop-PK model estimated a V_{ss} of 0.85 L/kg, leading to an under-estimation 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 BID atomoxetine in CYP2D6 PMs **39.**

The *in vitro* measured CYP3A4 K_i **40** 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 mg or 40 mg following BID administration in healthy CYP2D6 EMs and PMs with the observed clinical data **38, 39**.

A sensitivity analysis was performed to verify the *in vitro* measured CYP3A4 K_i **40** and fu_{mic} for atomoxetine, using midazolam as a substrate. Details of the study designs and results of atomoxetine model verification are shown in the Supplementary Information (S3).

The verified atomoxetine model was then applied to prospectively predict the interaction between trazodone and atomoxetine. Ten virtual trials of 10 subjects each (aged 20-50 years, proportion of female = 0.5) were generated. 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 BID for 12 days). The dose staggering of 2 hours was selected based on matching the simulated t_{max} of trazodone (~ 0.5 hr) and atomoxetine (~ 2.5 hr) 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 (pred:obs) PK parameters, such as 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 **41**. 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 mg, 60 mg 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 mg, 60 mg or 90 mg oral solution formulation of trazodone in healthy adults are presented in **Table 3** and **Fig 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 TID for 7 days in healthy adults

This simulation resulted in a mean C_{max} of 1822 ng/mL, compared with the clinically observed mean C_{max} of 3026 ng/mL. The predicted mean AUC_{0-24} was 24982 ng*h/mL compared with a clinically observed value of 32136 ng*h/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 TID **42** was not accounted for in the simulations. The slight under-estimation 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 h, 8 h and 1 h prior to and again at 8 h 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 over-estimation 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 **29**. Due to 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 optimised $fm_{CYP3A4,}$ 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**). Since 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 paediatric and adult C_{max} to relevant adult doses

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

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

- for 2-6 yr old group, doses of 0.35, 0.8 and 1.6 mg/kg QD
- for >6-12 yr old group, doses of 0.4, 1.0 and 1.9 mg/kg QD
- for >12-17 yr old group, doses of 0.4, 1.1 and 2.1 mg/kg QD

Simulations of 20 mg BID and 40 mg BID atomoxetine PK in healthy adults

The mean simulated C_{max} and AUC values for atomoxetine 20 mg BID were 171 ng/mL and 1180 ng*h/mL, respectively, in CYP2D6 EMs and 776 ng/mL and 8210 ng*h/mL, respectively, in PMs. The corresponding C_{max} and AUC observed values were 160 ng/mL and 1080 ng*h/mL, respectively, in EMs and 915 ng/mL and 8440 ng*h/mL, respectively, in PMs **39**. 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 BID were 355 ng/mL and 2025 ng*h/mL respectively in CYP2D6 EMs and 1608 ng/mL and 16602 ng*h/mL respectively in PMs. The corresponding C_{max} and AUC observed values were 527 ng/mL and 2590 ng*h/mL respectively in EMs and 1949 ng/mL and 18600 ng*h/mL respectively in PMs **38.** 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 under-predicted 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 paediatric doses of trazodone for its use in a paediatric clinical 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 since they arebased on body weight 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 **43**. Scaling by body weight (BW), body surface area (BSA) or $BW^{0.75}$ were tested for 30 different drugs. The BW scaling method under-predicted the majority of doses across the paediatric range. The BSA and $BW^{0.75}$ methods over-predicted some doses by up to 2.86 fold **44**. PBPK modelling was the method approved for dose prediction by the regulatory authority in this case, since it has the potential to integrate information from age-specific physiological and biochemical data, as well as data from pre-clinical, clinical and *in-vitro* sources to elucidate PK changes in children and complement paediatric studies and investigational plans **45.**.

The paediatric dose projection primarily focused on matching the equivalent steady-state C_{max} in adults, to minimise 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 paediatric population for dose prediction.

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

- 2-6 yr old group, doses of 0.35, 0.8 and 1.6 mg/kg QD, respectively;
- >6-12 yr old group, doses of 0.4, 1.0 and 1.9 mg/kg QD, respectively;
- >12-17 yr old group, doses of 0.4, 1.1 and 2.1 mg/kg QD, respectively.

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

10 children will be recruited in each of the age groups (2-6 yrs, >6-12 yr and >12-17yr) and stratified by age and dose level as follows:

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

The use of the doses predicted using PBPK modelling marked an important milestone towards 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 below. Firstly, 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 was 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 paediatric 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 maturation pattern for albumin (HSA) and for α_1-acid glycoprotein (AAG) are comparable in paediatrics > 2 years old **36**. 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 the paediatric 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. Since atomoxetine is frequently used in NDD, these predictions are reassuring and indicate that trazodone can be used concurrently with atomoxetine.

It can be concluded that the above predicted doses of trazodone can be used to guide dosing in the initial clinical trials in paediatrics as endorsed by the EMA (ref. EMEA-002142-PIP01-17), prior to conducting the first controlled clinical study in paediatrics. The conduct of a clinical trial in paediatrics is now in progress, based on the dose predictions above. Ethical and regulatory approval 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.

STUDY HIGHLIGHTS

What is the current knowledge on topic?

Paediatric insomnia is a common comorbidity in neurodevelopmental disorders (NDD). 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 doses of trazodone to guide dosing in a clinical trial on paediatric 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?

Paediatric doses of trazodone were predicted from commonly prescribed adult doses used in insomnia, using a PBPK strategy.

How might this change drug discovery, development, and/or therapeutics?

Currently there are no approved drugs for the treatment of paediatric insomnia in NDD. These predicted doses of trazodone were used to guide dosing in a Paediatric 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 co-administered.

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Legends for Figures

Fig 1: Summary of PBPK modelling strategy for predicting exposure of trazodone in children.

Fig 2: Predicted (black line represents mean and grey lines represent individual trials) and observed (circles – A, B, C, D: **31**; E: **32**; F: **25, 32**) trazodone plasma concentration profiles following administration of different doses and formulations.

Fig 3: Predicted median total plasma concentration-time profiles of trazodone following the respective predicted final doses in 2 to 6 years old; >6 to 12 years old and >12 to 17 years old. These were based on matching the adult C_{max} following 30 mg IR QD for 7 days (A and B); 75 mg IR QD for 7 days (C and D) 150 mg IR QD for 7 days (E and F).

Supplementary File

(Supplemental Material: Text.PDF)

Supplementary Information

Table 1. Input parameter values used to simulate the kinetics of trazodone

Parameter Name	Value	Method/Source
Physical Chemistry and Blood Binding		
MW (g/mol)	408.32	**19**
Log P	2.87	Calculated from experimental value of logD7.4 (=2.79) **20**
Compound type	Monoprotic Base	**20**
pK_a	6.61	Measured **20**
B/P	0.68	Calculated from measured E:P ratio of 0.2. **21**
fu_p	0.0354	Measured by equilibrium dialysis. **22**
Model	**Full-PBPK**	
Vss (L/kg)	1.0	Predicted (Method 2) **23**
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).**24**
k_a (hr^{-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) **24** ER: fitting of concentration-time data following a single oral dose of 300 mg ER trazodone **25**
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)

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

Parameter Name	Value	Method/Source
Phys Chem and Blood Binding		
MW (g/mol)	291.82	**38**
logP	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	**38**
Model	Minimal-PBPK	
Vss (L/kg)	0.71	Optimized; observed Vss is 0.85 L/kg
Absorption		
F_a	1	
K_a (hr^{-1})	0.926	Estimated by Pop-PK analysis **38**
fu_{gut}	1.0	Default
Elimination		
CL/F (L/h)	CYP2D6 EM: 26.4 (CV%: 55.7) CYP2D6 PM: 2.55 (CV%:18)	Estimated by Pop-PK analysis **38**
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)

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.h)**	**C_{max} (ng/mL)**	**AUC_{0-48} (ng/mL.h)**	**C_{max} (ng/mL)**	**AUC_{0-48} (ng/mL.h)**	**C_{max} (ng/mL)**	**AUC_{0-48} (ng/mL.h)**
Predicted mean	619.8	4660.3	387.9	2805.3	775.8	5610.5	1163.6	8415.8
Observed mean [31]	692	4970	446	2892	807	5610	1091	8811
Pred:Obs	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 BID 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	4470	812	9529	617	4455	850	12958
Observed mean [29,30]	681	4668	922	9275	842	5860	1125	13880
Predicted Ratio			1.28	2.09			1.39	3.14
Observed Ratio			1.35	1.99			1.34	2.37
Pred:Obs			0.95	1.05			1.04	1.32
Atomoxetine model verification using PK simulations of 20 mg BID and 40 mg BID in CYP2D6 EM and PM								
Dose	**20 mg BID : EM**		**20 mg BID : PM**		**40 mg BID : EM**		**40 mg BID : PM**	

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	171	1180	776	8210	355	2025	1608	16602
Observed mean	160	1080	915	8440	527	2590	1949	18600
Pred:Obs	1.07	1.09	0.85	0.97	0.67	0.78	0.83	0.89

Table 4: Final predicted paediatric doses corresponding to adult exposure following relevant doses.

Age Range (yr)	Median BW in the virtual population (kg)	Dose (mg/kg QD)	$AUC_{0\text{-}24h,\ Day\ 7}$ (ng/mL*h) Geometric Mean (95% CI)	$C_{max,\ Day\ 7}$ (ng/mL) Geometric Mean (95% CI)
Final predicted paediatric doses (QD) and PK parameters based on matching the adult trazodone C_{max} following 30 mg IR QD for 7 days				
2-6	16	**0.35**	1876.2 (1736.8-2026.8)	408 (395.2-421.2)
> 6 – 12	28	**0.4**	2060 (1897.5-2236.4)	400.5 (386.9-414.6)
> 12-17	51	**0.4**	2178.7 (2012.5-2358.6)	376.7 (362.8-391.1)
Adult	73	**30 mg**	2619.2 (2402.7-2855.3)	416.9 (398.8-435.7)
Final predicted paediatric doses (QD) and PK parameters based on matching the adult trazodone C_{max} following 75 mg IR QD for 7 days				
2-6	16	**0.8**	4304.6 (3963.3-4675.3)	945.9 (916.5-976.5)
> 6 – 12	28	**1.0**	4954.9 (4558.4-5385.8)	991.6 (959.3-1025.0)
> 12-17	51	**1.1**	5718.3 (5238.2-6242.5)	1037.5 (998.4-1078.2)
Adult	73	**75 mg**	6369.5 (5800.3-6994.7)	1025.2 (978.9-1073.6)
Final predicted paediatric doses (QD) and PK parameters based on matching the adult trazodone C_{max} following 150 mg IR QD for 7 days				
2-6	16	**1.6**	8609.3	1891.9

			(7926.7-9350.6)	(1833.0-1952.7)
> 6 – 12	28	**1.9**	9414.3 (8661.0-10233.1)	1884.1 (1822.6-1947.6)
> 12-17	51	**2.1**	10916.8 (10000.2-11917.5)	1980.7 (1906.0-2058.4)
Adult	73	**150 mg**	12739.1 (11600.6-13989.3)	2050.4 (1957.9-2147.3)