Precision dosing based optimisation of paroxetine during pregnancy for poor and ultra-rapid CYP2D6 metabolisers: a virtual clinical trial pharmacokinetics study

Running Title: Precision dosing based optimisation of paroxetine during pregnancy

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ABSTRACT

Background: Paroxetine has been demonstrated to undergo gestation related reductions in plasma concentrations, to an extent which is dictated by the polymorphic state of CYP 2D6. However knowledge of appropriate dose titrations is lacking.

Methods: A pharmacokinetic modelling approach was applied to examine gestational changes in trough plasma concentrations for CYP 2D6 phenotypes, followed by necessary dose adjustment strategies to maintain paroxetine levels within a therapeutic range of 20-60 ng/mL.

Key Findings: A decrease in trough plasma concentrations was simulated throughout gestation for all phenotypes. A significant number of ultra-rapid (UM) phenotype subjects possessed trough levels below 20 ng/mL (73-76 %) compared to extensive-metabolisers (EM) (51-53 %).

Conclusions: For all phenotypes studied there was a requirement for daily doses in-excess of the standard 20 mg dose throughout gestation. For EM, a dose of 30 mg daily in trimester 1 followed by 40 mg daily in trimesters 2 and 3 is suggested to be optimal. For poor-metabolisers (PM) a 20 mg daily dose in trimester 1 followed by 30 mg daily in trimesters 2 and 3 is suggested to be optimal. For UM, a 40 mg daily dose throughout gestation is suggested to be optimal.

KEYWORDS

Paroxetine; pharmacokinetics; PBPK; pregnancy; phenotype

1. INTRODUCTION

Depression in pregnancy is a serious and prevalent condition with incidence rates as high as 20 % [1]. Selective serotonin reuptake inhibitors (SSRIs) include antidepressants such as citalopram, fluoxetine, sertraline, paroxetine and fluvoxamine. Paroxetine is used to treat several conditions including major depressive disorder, social anxiety disorder, posttraumatic stress disorder, panic disorder, obsessive-compulsive disorder and anxiety disorder [2, 3]. Paroxetine has been given a category D banding by the FDA because of its increased risk of causing birth defects when taken during the first trimester, in addition to being associated with neonatal withdrawal syndrome when administered later in pregnancy [4]. Nevertheless, the potential harms of using paroxetine during pregnancy should be weighed carefully against the potential for serious risks of untreated maternal depression. This is particularly important given that recent reports in the UK have suggested that 1 in 25 women (aged 20-35 years) who die by suicide, do so during the perinatal periods (conception-pregnancy and post-natal) [5]. And further, that poor mental health during gestation is a highly correlated with poor mental health postnatally [6].

Paroxetine is primarily metabolised by Cytochrome P450 2D6 (CYP 2D6) and to a lesser extent (but equally important) by CYP 3A4, with minor roles for CYP 1A2, C219 and 3A5 [7]. Further, paroxetine is also a mechanism-based inhibitor of CYP 2D6 [8, 9], which results in a significant decrease in clearance under multiple-dosing (steady-state) conditions [10]. Further, several studies have noticed an apparent increase in the activity of CYP 2D6 during gestation which results in an approximate 50 % decrease in paroxetine plasma concentrations compared to pre-pregnancy levels [3, 11-15]. However, perhaps complicating the use of paroxetine during gestation, is the fact that CYP 2D6 is extensively polymorphic with at least a 7-fold difference in the median total clearance between the extensive metabolism (EM) and poor metaboliser (PM) phenotypes [10, 16]. Furthermore, the therapeutic window was assumed to be in the

range of 20-60 ng/mL [17, 18]. However, therapeutic blood concentrations for paroxetine can range from 10 ng/mL to 120 ng/mL [19], with toxicity reported to commence at approximately 350 ng/mL [20].

There are no well-controlled, large scale reliable studies of paroxetine use throughout gestation. However, the clinical toxicology database TOXBASE® (https://www.toxbase.org) [21], from the National Poisons Information Service Unit has published guidance for paroxetine use throughout pregnancy and suggest that paroxetine can be continued where an SSRI is considered clinically necessary and where paroxetine has been found to be the only effective agent. Further, the risks of continuing must be weighed against the possible negative outcomes associated with relapse [22]. It is important to consider the risks associated with any relapse as well the risk of relapse itself and recommendations are to use the lowest effective dose and for clinicians to follow this advice without risking relapse [22]. With this in mind, it is important that clinicians are aware of likely gestation-related variation in paroxetine levels [23].

In the context of post-natal period, paroxetine has been reported to lead to neonatal withdrawal syndrome, particularly persistent pulmonary hypertension of the new-born (PPHN) when paroxetine is used beyond 20 weeks gestation, but not amongst infants of mothers who used the drug prior to eight weeks [24]. However, this risk is thought to be small for the SSRI group as a whole [25].

Given that poor mental health during gestation is a highly correlated with poor mental health postnatally [6], the benefit of therapy should be weighed against the potential risk of cessation of therapy and the associated consequence for the mother and child [6, 26]. However, the requirement for adjustments of daily dosing duration gestation is uncertain.

In light of the paucity in pharmacokinetic data for paroxetine during gestation, we have, for the first time, applied the concept of pharmacokinetics-based virtual clinical trials dosing to elucidate possible dose adjustments that could be implemented in both EM and polymorphic CYP 2D6 subjects throughout gestation. The primary aim of this study was to use the principles of mechanistic pharmacokinetic modelling and virtual clinical trials to: (i) elucidate the causative effects of this decrease in plasma paroxetine levels during gestation and (ii) to provide a clinically relevant dosing adjustment strategy that could be implemented to maintain plasma paroxetine levels during gestation, when taking into consideration the CYP 2D6 phenotype status patients.

2. METHODS

The physiologically-based pharmacokinetic (PBPK) modelling tool Simcyp was utilised to conduct virtual clinical trials simulations in subjects (Simcyp Ltd, a Certara company, Sheffield, UK, Version 17). For studies in Step 1, simulations incorporated mixed genders (50:50), with studies in Step 2-4 utilising females only. A four-stage workflow approach was applied for the development, validation and simulation studies with paroxetine (Figure 1).

Adaptations to both the paroxetine 'compound file' and the Pregnancy 'population group' were made and described below.

2.1 Step 1: Validation of paroxetine

Within the virtual clinical trial simulator Simcyp, the 'healthy volunteer' (HV) population group was used to simulate 'non-pregnant' females as a baseline, with the 'pregnancy' population group utilised for all gestational studies. The pregnancy population group was developed by Simcyp, to included necessary gestational dependant changes in physiology, such

as blood volume and organ/tissue perfusion and enzyme/protein expression thought to play a role in altering the pharmacokinetics of drugs [27-30].

Paroxetine has been previously developed by Simcyp and incorporated into the Simcyp simulator [7]. However, to account for the impact of physiological alterations during gestation on paroxetine pharmacokinetics, a modification to the prediction of the volume of distribution at steady-state (Vss) was required, from a pre-set minimal-PBPK model to a full-body PBPK distribution model. This required the application of a Weighted Least Square (WLS) approach and the Nelder-Mead minimisation method to the calculation of Vss from a tissue-partition coefficient scaler (Kp scalar) [31]. The pharmacokinetics parameters used for paroxetine model are detailed in Supplementary Materials (Table S1).

Validation of the revision made to the paroxetine compound file employed three single dose studies and two multiple dose studies: (i) 28 male healthy volunteers (18-50 years old) dosed a single oral dose of 20 mg [32]; (ii) 9 healthy male subjects administered a single 20 mg oral dose of paroxetine [33]; (iii) 12 healthy volunteers aged between 20-35 years old (9 males, 3 females) administered a 20 mg single dose of paroxetine [34]; (iv) 28 healthy volunteers administered a 20 mg daily for 13 days, with sampling on days 12 and 13 [35]; (v) 7 healthy males administered a 20 mg oral dose of paroxetine daily for 3 days, with sampling on day 1 and 3 [36].

Simulation trial designs were run to match clinical studies used in validation.

2.2 Step 2: Validation of paroxetine during gestation

Paroxetine plasma concentrations have been reported during gestation from a retrospective analysis of therapeutic drug monitoring services in Norway [3], consisting of 29 serum drug concentrations during pregnancy and 31 drug concentrations at baseline (non-pregnancy

females) obtained from 19 women taking an oral dose of 20 mg daily. This data was extracted and utilised as 'observed' data for validation purposes. The Simcyp Pregnancy population group was adapted to incorporate CYP 2C19 activity modifications during gestation, details of which can be found in the Supplementary Materials Section 1. Further, the optimised Vss predicted from Step 1 was applied here, which was allowed to alter in line with maternal physiological changes during gestation.

In simulating paroxetine pharmacokinetics during gestation, a 38-week trial design was utilised, with simulations conducted using a 3x10 trial design with a daily oral dose of 20 mg daily for all subjects. Data was collected over the final 24 hours of every fifth week. The trial design was also replicated for healthy volunteer population of non-pregnant females (baseline) dosed under the same dosing strategy for comparison. Furthermore, changes in AUC and total *in-vivo* clearance were quantified during gestation.

2.3 Step 3: Phenotype simulation

To assess the impact of CYP 2D6 phenotypes on maternal paroxetine plasma concentrations, data was extracted from an observational cohort study in 74 pregnant women aged from 25 to 45 years who used paroxetine during pregnancy and where data was reported for gestational weeks 16–20, 27–31 and 36–40 [37]. The study included data from 43 extensive metabolisers (EM), 5 poor metabolisers (PM) and 1 ultra-rapid metaboliser (UM).

Simulations were conducted using a 10x10 trial design at GW 20, 30 and 38, with EM, UM and PM populations dosed 20 mg daily during gestation, and compared to results obtained from Simcyp.

2.4 Step 4: Dose adjustment during gestation

In order to identify the requirement for a dose adjustment during gestation, we examined the impact of dose escalation on paroxetine plasma concentrations. Doses were escalated in 5 mg increments every 3 days to 15-50 mg daily doses during gestation, with trough plasma concentrations analysed for the final day of each trimester.

Data was collected and reported for the EM, PM and UM phenotype. The percentage of subjects with trough plasma concentrations below 20 ng/mL and above 60 ng/mL were quantified for each trimester and each phenotype.

2.5 Predictive performance

For all simulations in steps 1-3, a prediction of a pharmacokinetic metric to within two-fold (0.5-2.0 fold) of that published clinical data was generally accepted as part of the 'optimal' predictive performance [38-40].

2.6 Visual predictive checks

Model predictions in step 1-3 were compared to clinical studies using a visual predictive checking (VPC) strategy [41]. In this approach, the predicted mean/median and 5^{th} and 95^{th} percentiles of the concentration–time profiles (generated from Simcyp) were compared against the observed data for any validation data sets. The prediction was assumed to be valid when the predicted data points overlapped with the observed data sets.

2.7 Data and statistical analysis

All observed data obtained from clinical studies were extracted using WebPlotDigitizer v.3.10 (http://arohatgi.info/WebPlotDigitizer/). Statistical analysis was conducted using a non-parametric Kruskal-Wallis with a Dunn's multiple comparison post-hoc test. Statistical significance was confirmed where $p < 0.05$ was determined. All statistical analysis was performed using GraphPad Prism version 7.00 for Windows (GraphPad Software, La Jolla California USA, www.graphpad.com).

3. RESULTS

3.1 Step 1: Validation of a revised paroxetine full-body PBPK model

A validated paroxetine model, developed and incorporated into the Simcyp Simulator, was utilised with adaptations to include a full-PBPK model for determination of appropriate Vss and to model physiological changes during gestation. The model was validated against a range of published clinical studies using the Simcyp healthy volunteer population group. For all single dose studies (Figure 2A and 2B) and multi-dose studies (Figure 2C), the simulated plasma concentration-time profiles were successfully predicted to within the observed range for each study and model-predicted t_{max}, C_{max}, and AUC were predicted to within 2-fold of the reported parameters for each study, confirming successful validation (Table 1).

3.2 Step 2: Validation of paroxetine during gestation

Model predicted plasma concentrations during gestation overlapped with the range of observations reported [3] during the entire period of gestation (Figure 3). The mean at baseline, 24.05 ng/mL ± 15.45 ng/mL, decreased for trimesters 1 (week 5: 21.51 ng/mL ±

12.93 ng/mL), 2 (week 20: 18.09 ng/mL ± 11.72 ng/mL) and 3 (week 30: 17.16 ng/mL ± 11.05 ng/mL), with a statistically significant decrease from week 15 onwards to week 35 ($p < 0.05$).

Given the polymorphic nature of the primary metabolic pathway of paroxetine (CYP 2D6), the changes in both clearance and AUC were further assessed during gestation for EM, PM and UM phenotype subjects within the heterogeneous healthy volunteer population generated by Simcyp (default Caucasian frequencies: EM: 86.5 %, PM: 8.2 % and UM: 5.3 %).

For both EM and PM, statistically significant differences in the AUC were apparent from gestational week (GW) 15 (EM) and GW10 (PM) onwards, respectively and GW25 for UM when compared to baseline subjects (Figure 4) (Supplementary Materials: Table S2 and S3). For CL, statistically significant differences for both EM and PM were evident from GW10 onwards and week 20 for UM. (Supplementary Materials: Table S2 and S3) (Figure 4).

For UM the AUC and CL demonstrated a 70-80 % decrease and 450-480 % increase in trimester 3 when compared to baseline, respectively (Figure 4). This is in comparison to EM where a 19-22 % decrease and 16-18 % increase in AUC and CL were noted from baseline, in trimester 3, respectively (Supplementary Materials: Table S2) (Figure 4).

3.3 Step 3: The impact of CYP 2D6 phenotypes on paroxetine levels during gestation

The effect of CYP 2D6 phenotypes on maternal paroxetine plasma concentrations during pregnancy were subsequently directly explored. Paroxetine plasma concentrations have previously been reported in CYP 2D6 phenotyped subjects [37]. To validate the ability of the model of recapitulate the impact of CYP 2D6 phenotypes (EM, PM and UM) on paroxetine levels, we compared model predictions of uniform singular phenotype population to those reported [37]. For EM, the predicted range of paroxetine plasma concentration (determined from the range of simulated maximum and minimum values), where within the range reported (Figure 5A). For PM (Figure 5B) and UM (Figure 5C), despites there being a limited number of reported values plasma concentration measurements available, predicted paroxetine vales were generally within or spanning the range reported [37] (Figure 5).

Within each phenotype, a decrease in both peak and trough concentrations were noted (Table 2), with the UM phenotype resulted in a significant number of subjects possessing trough levels below 20 ng/mL (73-76 %) compared to EM (51-53 %) (Table 2).

3.4 Step 4: Paroxetine dose optimisation

To identify appropriate dose adjustments during gestation for CYP 2D6 phenotypes, the number of subjects with trough concentration below 20 ng/mL and above 60 ng/mL were quantified over the dosing range of 15-50 mg daily.

In all phenotypes studies (EM, PM and UM), the daily dose required was in excess of the standard 20 mg/day throughout gestation. The choice of optimal dose was based around ensuring a balance of a low percentages of subjects with plasma levels below 20 ng/mL or above 60 ng/mL. In order to accomplish this, a suggested indicator of 20 % was used to ensure,

where possible, as many subjects as possible had trough concentration above 20 ng/mL in addition to being below 60 ng/mL (Figure 6).

For EM, a dose of 30 mg daily in trimester 1 followed by 40 mg daily in trimesters 2 and 3 is suggested to be optimal. For PM a 20 mg daily dose in trimester 1 followed by 30 mg daily in trimesters 2 and 3 is suggested to be optimal. For UM, a 40 mg daily dose throughout gestation is suggested to be optimal

In determining the appropriate dose, the 40-50 mg/d doses resulted in the highest individual trough concentration in the range of 200-300 ng/mL for the trial group (Supplementary Materials: Table S4).

4. DISCUSSION

Depression is far more prevalent in women than men [42, 43], and is the leading cause of disability worldwide [44]. Furthermore, the prevalence of depression during pregnancy is thought to be in excess of 10 % [45], however the use of mental health services by pregnant women is low, approximately 14 %, when compared to non-pregnant women, approximately 25 % [46]. The use of pharmacological treatment for mental health disorders during pregnancy is governed by balancing the risk to the foetus alongside the risk of relapse in the mental health of the mother.

Confounding treatment however, are gestation related alterations in maternal physiology which can impact upon the pharmacokinetics of drugs. These alterations include the reduction in intestinal motility, increased gastric pH, increased cardiac output, reduced plasma albumin concentrations, and increased glomerular filtration rate [47]. However, the consequences of such alterations are often difficult to ascertain in controlled trials for obvious ethical reasons,

which leaves prescribers to empirically treat pregnant patients according to their understanding of the changes in biochemical and physiologic functions [14].

However, to assess the potential impact of pregnancy on antidepressant therapy, the use of robust and validated mechanistic pharmacokinetic models provides an opportunity to prospectively assess the potential changes in a drugs pharmacokinetics to support medicines optimisation.

Paroxetine is primarily metabolised by CYP2D6 and to a lesser extent by CYPs 3A4, 1A2, C219 and 3A5 [7]. Further, paroxetine is also a mechanism-based inhibitor of CYP 2D6 [8, 9], which results in a significant decrease in clearance under steady-state conditions [10]. The use of paroxetine duration gestation is complicated by the fact that several studies have noticed an apparent increase in the activity of CYP 2D6 during gestation [11-15], with an associated decrease in paroxetine plasma concentration during gestation, by up to 50 %, in comparison to non-pregnant females [3].

Given the lack of more detailed clinical studies examining this phenomenon, for the first time this study applied the principle of pharmacokinetic modelling to prospectively assess the use of paroxetine in pregnancy population groups and attempted to relate changes in plasma concentrations during gestation to a potential therapeutic window region. The Simcyp pregnancy PBPK model has been utilised by our group and others for prediction of the impact of changes in plasma concentrations associated with gestation [28, 31, 48], however this is the first time it has been utilised in the context of paroxetine.

The development of the model utilised an existing, validated and published model of paroxetine within the Simcyp Simulator, with minor modification to allow it to be used in the context of pregnancy, particularly to account for the impact physiological changes in gestation on paroxetine pharmacokinetics. This was accomplished by utilising paroxetine

within a full-body physiologically based pharmacokinetics (PBPK) model. This adaptation required validation against single and multiple dose studies in non-pregnant subjects (Step 1) followed by pregnant subjects (Step 2). Resulting predictions in non-pregnant subjects, were within 2-fold of those reported along with appropriate VPC confirming population level variability in plasma concentrations (Figure 2) were appropriately predicted in relation to the clinically reported variability (Table 1).

There is currently a paucity of pharmacokinetics data examining the impact of gestation on paroxetine plasma concentrations. To our knowledge, Westin *et al* [3] is the only publication (to date) containing paroxetine plasma concentrations sampled in patients throughout gestation. This was therefore used as the basis for validating the paroxetine pregnancy PBPK model. Simulations were conducted for the entire gestation period (38 weeks) and sampling and quantification conducted on the final day of each week for every 5^{th} week during gestation (Weeks 0-35) (Figure 2). In non-pregnant subjects ('baseline'), the predicted plasma concentrations (24.05 ng/mL ± 15.45 ng/mL) were within 2-fold of those reported by Westin *et al* [49] (33.5 ng/mL) (Table 2) and further spanned across a similar range of reported values. Westin *et al* [3] reported a 12 %, 34 % and 51 % decrease in mean plasma concentration at for trimesters 1-3, respectively. Using the PBPK model we demonstrated a similar decrease of up to 30% by trimester 3 (Figure 2).

In order to understand the rationale for the decrease in paroxetine plasma levels during gestation, we further assessed changes in total (*in-vivo*) clearance and AUC. This was demarked for the CYP 2D6 phenotype of each subject. In all phenotypes, the clearance increased during gestation, which mirror the increase in 2D6 activity reported during gestation [14], with the greatest difference in clearance occurring in trimester 3 (Supplementary Materials: Table S2). This increase in clearance would therefore reduce the overall bioavailability within subjects, as demonstrated by the statistically significant difference in the

AUC in trimester 3 for all phenotypes (Supplementary Materials: Table S2). Within each phenotype, the UM subjects demonstrated the greatest difference in both clearance and AUC during gestation.

The decrease in plasma concentrations noted in our study concurs with previous reports [14, 37], and may be associated with temporal changes in CYP 2D6 expression (induction) noted throughout gestation [15]. Ververs [37] reported an increase in PM plasma concentration [37] during gestation, which is in contrast to the reduction modelled within our studies. However, the number of PM subjects in their study, n=1, is low making it difficult to extrapolate to a larger cohort of PM subjects in a generalised fashion.

Given the importance of the phenotype of the subject on gestational paroxetine levels, we next explored the ability of the model to correctly capture phenotype levels and also to examine the tough levels in the context of the therapeutic window. Paroxetine plasma concentrations have previously been reported in CYP 2D6 phenotyped subjects [37], of which the EM, PM and UM were investigated using uniform singular phenotype populations. Ververs reported single point levels which were sampling at non-specific intervals post-dosing [37] and therefore comparison were made to C_{max} and C_{min} levels in each subject simulated in our studies. For both EM (Figure 5A) and PM (Figure 5B), model predicted levels spanned the range of reported levels across gestational weeks (Figure 5). For the UM phenotype population, only 3 observed samples were available across gestation (Figure 5C). Although the predicted levels spanned some of the predicted levels, the lack of UM data precludes a full comparison to be made (Figure 5).

For the PM phenotype, as a result of a loss of function alleles, gestational changes in paroxetine pharmacokinetics would be primarily governed by maternal physiological alterations or alternative clearance pathways, e.g. CYP 3A4, whose activity is known to increase during

gestation [50], rather than direct changes in CYP 2D6 expression. Thus, the combined impact of minimal CYP 2D6 mediated clearance (in PM phenotypes), but enhanced CYP 3A4 clearance due to gestational induction, may result in a potential net minimal changes in plasma levels during gestation [48].

To assess the potential impact of these polymorphic subjects on possible sub therapeutic levels, we quantified the percentage of subjects with trough concentration below the lower therapeutic window (20 ng/mL). The UM group demonstrated significantly larger percentages below 20 ng/mL when compared to the EM group (Supplementary Materials: Table S4), > 70 % from week 20 onwards. Whereas for the PM group, this remained at 34 % from week 20 onwards. Given this variability, we next examined how a dose adjustment could be made for EM, PM and UM subjects throughout gestation.

For all phenotypes studies (EM, PM and UM), there was a requirement for daily doses in-excess of the standard 20 mg dose throughout gestation. Whilst there is some uncertainty as to the upper most limit of the therapeutic window (60-350 ng/mL) [19, 20, 51], the lower window was used as a reference point for dose optimisation with trough levels.

For EM, a dose of 30 mg daily in trimester 1 followed by 40 mg daily in trimesters 2 and 3 is suggested to be optimal. For PM a 20 mg daily dose in trimester 1 followed by 30 mg daily in trimesters 2 and 3 is suggested to be optimal. For UM, a 40 mg daily dose throughout gestation is suggested to be optimal

The PM phenotype has been shown to require more frequent switches and dose modification [52] due to an increase in the frequency and severity of associated concentration-dependent adverse effects [53], resulting in an approximate 4-fold increase in the risk of discontinuation during pregnancy [54]. This makes appropriate dose modification difficult in women who are already experiencing adverse effects during gestation, such as nausea from morning sickness

in addition to nausea as an SSRI adverse drug reaction. Further, for the UM group, this cohort would be at greater risk of sub-therapeutic paroxetine plasma concentration without a dose adjustment, resulting in an increase in depressive symptoms, as has been recently noted in a retrospective analysis of phenotyped pregnant women taking anti-depressant drugs during gestation [54].

The outcomes of the dose optimisation study identified that a dose increase would be required throughout gestation, irrespective of the phenotype. With EM requiring an increase to 30-40 mg daily, PM 20-30 mg daily and UM 40 mg daily. In all of these cases, the percentage of subjects with sub-therapeutic concentrations (<20 ng/mL) would be less than 20 %. Post-natal dose tapering would be required to return maternal plasma levels to those in the pre-natal period. Whilst the capability of simulating the return of maternal physiology to the pre-natal period is not possible within Simcyp, Nagai *et al* (2013)[55] have suggested a tapering dose decrease of 10 mg per week commenced before delivery, based upon transplacental paroxetine transfer and pharmacokinetic modelling, may be effective in reducing the incidence of withdrawal symptoms in the neonate and mother. However, paroxetine has a very short half-life (compared to other SSRIs) and discontinuation phenomena are a concern. Clinicians should be encouraged to be alert for these during dose tapering as they would in any other dose-reduction phase with SSRIs.

It should be noted that given paroxetine is administered orally, changes in gestational gastric physiology such as delayed gastric emptying [56, 57] and alterations in gastric pH [58] may alter the absorption of paroxetine *ab orally*, studies have demonstrated that given paroxetine is completely absorbed [59, 60], changes in GI-physiology during gestation are likely to have a minimal effect. Further, paroxetine oral absorption is unaffected by changes in gastric pH [61] negating the potential impact of changes in paroxetine ionization and dissolution *ab orally* during gestation. However gestational related changes in material GI-physiology are not

currently incorporated in the Simcyp Simulator utilised within this study. Nevertheless, the utilising of robust validation approaches allowed for the pragmatic assessment of the need for dose adjustment during gestation, however further confirmatory clinical studies are warranted to confirm the results presented within this study.

5. CONCLUSION

The decision to continue or withdraw antidepressants during pregnancy is challenging when considering the paramount importance of both maternal and neonatal health. The prescriber must actively decide whether the benefit of continuing treatment outweighs any risk of the drug to the developing embryo/foetus. If treatment is continued throughout pregnancy, the changes in maternal physiology should be considered in dosing strategies. With paroxetine, this is further confounded given its susceptibility to CYP 2D6 polymorphism. Based upon modelling studies, our findings suggest that optimisation of paroxetine during pregnancy requires dose increase when compared to non-pregnant patients, driven by changes in tissue physiology and its impact on the volume of distribution, in addition to gestation related alterations in CYP isozyme abundance. For UM phenotypes, at least a doubling in the dose is required to provide a plasma concentration within the therapeutic range.

Although there is no requirement for genetic testing prior to initiation for SSRIs, our approach highlights the opportunity for pharmacokinetics to bring precision dosing into clinical practice. Pre-emptive genotyping may be an approach to support precision dosing in pregnancy to optimise drug therapy and to reduce the risk of relapse due to inadequate dosing.

However, further studies are required to assess both the extent of this gestational change on plasma concentrations and any associated requirement for dose adjustment, in addition to also

identifying a more accurate therapeutic range to more precisely define the necessary dose adjustments.

Funding

This work was supported by Kuwait University.

Declaration of conflicting inflects

The Author(s) declare(s) that there is no conflict of interest.

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Figure 1. A four-stage workflow based approach to paroxetine modelling

Figure 2. Simulated paroxetine plasma concentrations following single and multiple dosing.

(A) Single 20 mg oral dose of paroxetine [32, 34]; (B) Single oral 20 mg dose with observed data presented as multiple sampling [33]; (C) Multiple daily 20 mg oral dose [35, 36]. Solid lines represent mean predicted concentration-time profile with dotted lines representing 5^{th} and 95^{th} percentile range. Solid circles represent observed clinical data from each study with error bars indicating standard deviation.

Figure 3. Simulated paroxetine plasma concentrations during gestation

Paroxetine plasma concentrations were simulated during gestation (n=30). Simulated concentrations represent post-dose trough concentrations (sampled at 24 hours after dosing) and collated at 5-week intervals over the gestation period (black open circles). Subjects were administered a 20 mg daily dose. 'Baseline' refers to non-pregnant females. Red open circles represent observed (pooled) plasma concentrations obtained from a total of 19 subjects. Shaded regions between 20 ng/mL to 60 ng/mL represents the therapeutic window.

Figure 4. Impact of gestation on paroxetine pharmacokinetics, demarked by CYP 2D6 population phenotype status.

612 The impact of gestation on paroxetine (A) area under the curve (AUC) and (B) clearance at
613 baseline (non-pregnant females) and during gestation. Data is demarked for the population
614 (n=100) phenotype status with black circles representing EM, red circles representing UM and
615 green circles represented PM. Solid coloured line represents median value.

616

617 **Figure 5. Simulated paroxetine plasma concentrations for CYP 2D6 polymorphs.**

618 Paroxetine peak (C_{max}) and trough (C_{min}) plasma concentration were simulated in CYP 2D6
619 EM (A), PM (B) and UM (C) subjects at gestations week 20, 30 and 38. Simulations
620 concentrations were compared to reported plasma concentration (red open circles) for each
621 phenotype. Blue circles: C_{min} of each subject; green circles: C_{max} of each subject.

622

623 **Figure 6. Phenotype-based dose optimisation of paroxetine during gestation.**

624 Paroxetine doses were escalated in 5 mg increments every 3 days to 15-50 mg daily does during
625 gestation, with trough plasma concentrations analysed for the final day of each trimester in
626 entirely EM, PM or UM pregnancy population groups. The number of subjects with trough
627 plasma concentration below 20 ng/mL (left panels) or above 60 ng/mL (right panels) are
628 reported.

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Table 1: **Summary pharmacokinetics parameters from the single and multiple dose studies**

	Dosing	PK Parameters	Observed	Predicted
Single	Segura *et al* (2003)[33]	$AUC_{(0\text{-}24\ h)}$	96.50 (65.90)	156.83 (138.69)
		C_{max}	8.60 (5.50)	11.10 (8.87)
		tmax	5 (3-5)	3.9 (1.72)
	Yasui-Furukori *et al* (2007)[34]	$AUC_{(0\text{-}48\ h)}$	127 (67)	230.3 (222.34)
		C_{max}	6.5 (2.4)	11.10 (8.87)
		tmax	5 (4-10)	3.9 (1.71)
	Massaroti *et al* (2005)[32]	$AUC_{(0\text{-}120\ h)}$	225.04 (291.91)	312.34 (347.90)
		C_{max}	9.02 (8.82)	11.10 (8.87)
		tmax	5.03 (1.91)	3.89 (1.71)
Multiple	Segura *et al* (2005)[36]	$AUC_{(0\text{-}8\ h)}$ [Day 1]	53.8 (26.7)	65.37 (53.52)
		$AUC_{(0\text{-}8\ h)}$ [Day 8]	159.8 (49.8)	205.76 (104.80)
		C_{max} [Day 1]	10.4 (4.8)	11.09 (8.87)
		C_{max} [Day 8]	26.1 (7.1)	31.61 (15.18)
		tmax [Day 1]	3 (3–5)	3.87 (1.62)
		tmax [Day 8]	8 (3–8)	4.15 (0.83)

AUC= Area under the curve, C_{max} = Maximum plasma concentration, tmax= time at maximum plasma concentration. Data represents mean (standard deviation). AUC: ng/mL.h; C_{max}: ng/mL; tmax: h.

638 **Table 2. Simulated paroxetine plasma concentrations during gestation**

	Week	C_{max} (ng/mL)	C_{min} (ng/mL)	Trough % < 20 ng/mL (% subjects)
	20	39.875 (129.6-2.45)	19.63 (0.15-91.87)	51
EM	**30**	37.235 (2.01-122.28)	18.765 (0.14-87.64)	53
	38	36.56 (1.88-120.04)	18.82 (0.15-86.16)	53
	20	46.535 (18.95-147.25)	25.225 (6.06-109.49)	34
PM	**30**	43.77 (17.62-139.78)	24.345 (6-105.09)	34
	38	42.85 (17.21-136.98)	24.435 (5.99-103.05)	34
	20	34.4 (0.55-110.91)	12.465 (0.04-73.3)	73
UM	**30**	31.69 (0.45-103.66)	11.665 (0.04-69.13)	76
	38	30.84 (0.42-102)	11.985 (0.04-68.22)	76

639

640 Data represents mean (range). EM: extensive metabolises; PM: poor metabolisers; UM:
641 ultrarapid metabolisers; C_{max}: maximum plasma concentration; C_{min}: minimum plasma
642 concentration.