

1 **Quetiapine dose optimisation during gestation: a pharmacokinetic modelling study**

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23 **ABSTRACT**

24 **Objectives:** The second generation antipsychotic quetiapine has been demonstrated to undergo  
25 gestation related changes in pharmacokinetics. This study applied pharmacokinetic modelling  
26 principles to investigate the mechanism of these changes and to propose new dosing strategies  
27 to counteract these changes

28 **Methods:** A pharmacokinetic modelling approach was implemented using virtual population  
29 groups. Changes in quetiapine trough plasma concentration during gestation were quantified  
30 across all trimesters and dose adjustment strategies were applied to counteract these changes  
31 by targeting a therapeutic range of 50-500 ng/mL throughout gestation

32 **Findings:** The application of the model during gestation predicted a decrease in trough  
33 concentration. A maximum decrease of 58 % was predicted during trimester 2, and being  
34 associated with a statistically significant decrease in oral clearance at gestation week 25, 204  
35 L/h  $\pm$  100.8 L/h compared to non-pregnant subjects, 121.9 L/h  $\pm$  51.8 L/h. A dosing  
36 optimisation strategy identified that dose increases to 500-700 mg twice daily would result in  
37 32-55 % of subjects possessing trough concentration in excess of 50 ng/mL.

38 **Conclusions:** Quetiapine doses in pregnancy should be increased to 500-700 mg twice daily to  
39 counteract a concomitant increase in metabolic clearance, increase in volume of distribution  
40 and decrease in plasma protein binding.

41

42 **KEYWORDS**

43 Quetiapine; pregnancy; pharmacokinetics; PBPK; dose optimisation.

## 44 1. INTRODUCTION

45 Quetiapine is a second generation antipsychotic that was first approved by the US Food and  
46 Drug Administration (FDA) in 1997 for the management of schizophrenia in both adults and  
47 adolescents in addition to a range of other psychiatric disorders [1, 2].

48 Several reports have highlighted that quetiapine is the most commonly prescribed atypical  
49 antipsychotic in women of childbearing age [3-5]. A key advantage of quetiapine over other  
50 atypical antipsychotics is that it is unlikely to be associated with extrapyramidal symptoms and  
51 is prolactin (PRL)-sparing but is associated with weight gain [6].

52 However, the use of pharmacological interventions for psychiatric disorders during pregnancy  
53 is particularly challenging, given the need to balance stabilisation of maternal mental state with  
54 the potential teratogenic effects of the prescribed drug. Often, this results in the cessation of  
55 treatment during the gestational period, particularly in trimester 1 [7].

56 In the wider context of pregnancy, approximately 15 % of women have some form of  
57 psychiatric illness with up to 13 % of women taking prescribed psychotropic pharmacological  
58 interventions [8, 9]. Clinicians are likely to be faced with the possibility of treatment (or not)  
59 within the perinatal setting. However, clinical studies have demonstrated that pregnancy should  
60 be considered as a 'high-risk' period for relapse in the context of a discontinuation of any  
61 maintenance treatment options [10-14]. This is particularly important given that recent reports  
62 in the UK have suggested that 1 in 25 women (aged 20-35 years) who die by suicide, do so  
63 during the perinatal periods (conception-pregnancy and post-natal) [15]. And further, that poor  
64 mental health during gestation is highly correlated with poor mental health postnatally [14].

65 Mounting evidence supports the notion that cessation of therapy during pregnancy may be  
66 detrimental to the mother for some antipsychotics, a choice which requires consideration of the  
67 risks and benefits of pharmacological interventions during gestation [7, 16, 17]. Although the  
68 risks of antipsychotic use during pregnancy may be outweighed by the clinical benefits,  
69 gestation brings about significant changes in the physiology of the mother which can have  
70 drastic changes on the pharmacokinetics of drugs administered during pregnancy. Quetiapine  
71 is primarily metabolised by the phase-1 Cytochrome P450 enzyme CYP 3A4 [18], and  
72 gestation can result in a significant increase in the expression of CYP3A4 [19-21] by between  
73 25-40 % [22], which would enhance quetiapine metabolic clearance and hence results in a net  
74 reduction in quetiapine plasma concentrations. An obvious change occurs in body composition  
75 with a 40-50 % increase in plasma volume [23, 24] throughout gestation along with a

76 concomitant increase in body fat, approximately 4 kg, resulting in alterations of the volume of  
77 distribution of hydrophilic and lipophilic drugs during gestation which would generally reduce  
78 plasma drug concentration. In addition, decreases in the plasma-proteins albumin and alpha-1-  
79 acidic glycoprotein will in turn increase the free drug fraction and directly influence the volume  
80 of distribution [25-27].

81 In a recent retrospective study, the plasma levels of a range of antipsychotics were analysed  
82 during gestation and it was identified that significant decreases in serum levels were evident,  
83 particularly for quetiapine, which decreased by up to 70 % in trimester 3 [28].

84 At present, there are no well-controlled or reliable studies of quetiapine use during pregnancy,  
85 and because of this reason the FDA have classified quetiapine as a category C drug, suggesting  
86 it should be used during pregnancy only if the benefits to the mother outweigh any risks to the  
87 patient. However, the US Office of Paediatric Therapeutics conducted a review of 220 adverse  
88 reports associated with quetiapine, which were submitted to the FDA adverse event reporting  
89 systems and identified that there doesn't seem to be a risk of congenital anomalies but  
90 acknowledge the limited nature of the data reported [29]. Further, the clinical toxicology  
91 database TOXBASE® (<https://www.toxbase.org>) from the National Poisons Information  
92 Service Unit [30], has provided guidance for the use of quetiapine during gestation and does  
93 not advocate its cessation necessarily, rather places emphasis on the consideration of the risk  
94 of relapse on cessation compared to the benefits to the mother and child during gestation.

95 We have, for the first time, applied the principles of mechanistic pharmacokinetic modelling  
96 and virtual clinical trials to better elucidate the causative effects of this decrease in plasma  
97 quetiapine levels during gestation, to provide a clinically relevant dosing adjustment strategy  
98 that could be implemented to maintain plasma quetiapine levels during gestation.

99 The objectives of this study were to: (i) develop a robust and validated pharmacokinetic model  
100 for quetiapine; (ii) identify a suitable therapeutic window for quetiapine and (iii) explore the  
101 impact of gestation on quetiapine plasma levels and address any alterations with clinically  
102 appropriate dose adjustments.

103

## 104 2. METHODS

105 Simulations were performed using the virtual clinical trial simulator Simcyp (Simcyp® Ltd, a  
106 Certara company, Sheffield, UK, Version 16). The ‘Healthy Volunteer’ population group was  
107 used for ‘non-pregnant’ females and the ‘Pregnancy’ population group utilised for all  
108 ‘pregnancy’ studies. The latter population group included necessary gestational dependant  
109 changes in physiology, such as blood volume and organ/tissue perfusion and enzyme/protein  
110 expression, which are thought to play a role in altering the pharmacokinetics of drugs [31-34].  
111 A 4-stage modelling approach was implemented. A previously validated model of quetiapine  
112 [35] was utilised with adaptations through the inclusion of CYP3A5 metabolic clearance  
113 pathway [36, 37].

114

### 115 2.1 Step 1: Validation of quetiapine

116 In order to implement a pregnancy model within Simcyp the previously validated quetiapine  
117 model [35] required modification as the model primarily implemented a minimal-PBPK model,  
118 which does not allow consideration of a distinct foetal/placental tissue compartment and  
119 physiological alterations in other maternal tissues during gestation. For simulations in pregnant  
120 subjects, a full-PBPK distribution model was required and therefore tissue-partition coefficient  
121 ( $K_p$ ) estimates were calculated using the Rogers and Rowland approach [38, 39]. These were  
122 then parameter estimated (using a Weighted Least Square (WLS) method and the Nelder-Mead  
123 minimisation approach) through the optimisation of a tissue partition coefficient scalar,  $K_{p_{\text{scalar}}}$ ,  
124 using a total of 3 single dose studies and 1 multi-dose study: (i) 12 men (24-42 years old) dosed  
125 a single oral dose of 25 mg [40]; (ii) 15 men and 3 women (29-63 years old) dosed at 25 mg  
126 twice daily on day 1, 50 mg twice daily on day 2, 100 mg twice daily on day 3, 200 mg twice  
127 daily on day 4 and 300 mg twice daily on day 5 until day 10 [40]; (iii) 10 men (35-55 years  
128 old) dosed at 25 mg three times daily (TID) (6 am, 2 pm and 10 pm) on day 1 and dose escalated  
129 to 50 mg TID on day 2, 75 mg TID on day 3, 100 mg TID on day 4 and by 50 mg increments  
130 daily until 250 mg TID on days 7 and 8 [41]; (iv) 11 men and 2 women (19-58 years) dosed at  
131 25 mg twice daily (BD) on day 1 and dose escalated to 50 mg BD on day 2, 75 mg BD on day  
132 3, 100 mg BD on day 4 and by 50 mg increments daily until 300 mg BD on 8 until day 21 [42].

133

134 Model simulations were run to match the reported age range and patient number reported by  
135 each study. However, in the absence of this information, a default trial size of 100 subjects  
136 (10x10 design) aged 20-40 years old was used.

137 Quetiapine model parameters can be found in Supplementary Materials: Section 1.

138

139

## 140 **2.2 Step 2: Validation of CYP3A5 metabolic clearance modification**

141 To further validate the appropriateness of modifications made to the CYP3A5 intrinsic  
142 clearance [37], three retrospective clinical drug-drug interactions studies were used to further  
143 validate the model and consisted of: (i) ketoconazole dosed alone for days 1 to 3 and in  
144 conjunction with quetiapine on day 4 [40]; (ii) quetiapine dose escalated to 300 mg twice daily  
145 by day 5 and maintained for 34 days. Thereafter carbamazepine initiated with a 200-mg dose  
146 on the evening of day 9, followed by 200 mg twice daily on days 10- 12, and increased to 200  
147 mg three times daily from days 13-33 with a final dose on the morning of day 34 [40] and (iii)  
148 quetiapine dose escalated from 25 to 250 mg three times daily by day 10 and maintained until  
149 day 23 with phenytoin administered at 100 mg three times daily on days 13-33 in conjunction  
150 with quetiapine [41].

151 Where possible, trial design and sampling duration was replicated from the original studies.

152

## 153 **2.3 Step 3: Validation during gestation**

154 A recent report by Westin *et al* [28] retrospectively collated serum level of antipsychotics  
155 before, during and after pregnancy. Data for quetiapine consisted of 66 measurements during  
156 pregnancy, 11 during the first 12 weeks following pregnancy and 144 at baseline, from 33  
157 women. Subjects were stabilised on 400 mg/daily. This data was extracted, pooled and utilised  
158 as 'observed' data for validation purposes.

159 In simulating quetiapine pharmacokinetics during gestation, a 38-week trial design was  
160 utilised, with simulations conducted using a 10x10 trial design with dosing adjusted on a daily  
161 basis by 50 mg/day to 200 mg twice daily for all subjects.

162 For all dosing approaches in pregnancy, unless otherwise stated, the pre-dose (trough) plasma  
163 concentration was ascertained 10 hours following each dose. For assessment of plasma  
164 concentration, all concentrations were dose adjusted to the defined daily dose (DDD), whereby  
165 the simulated plasma concentration was divided by the daily dose and subsequently multiplied  
166 by the DDD (the average maintenance dose per day for its main indication in adults)[43].

167 For comparison, the trial design was also replicated for Healthy Volunteer population of non-  
168 pregnant females dosed under the same dosing strategy.

#### 169 **2.4 Step 4: Dose adjustment during gestation**

170 Limited data currently exists purporting to show a relationship between plasma quetiapine  
171 levels and clinical responses and these have recently been summarised in a review by Mauri et  
172 al (2018) [44]. Further, a suggested therapeutic window of between 100-500 ng/mL has been  
173 proposed by the Arbeitsgemeinschaft für Neuropsychopharmakologie und  
174 Pharmakopsychiatrie (AGNP) [45] and this was adopted as the potential therapeutic window.  
175 However, the region of 50-100 ng/mL was also considered as a 'borderline' range, given that  
176 doses in the range of 150-800 mg daily can yield mean trough concentrations in the range of  
177 27-387 ng/mL [46-50]. Although the FDA advocated maximum recommended dose is 800 mg  
178 daily [51], a number of studies have assessed the safety of higher doses in non-pregnant  
179 subjects to a maximum of 1400 mg daily [52-54] with no significant safety concerns.

180 In a recent case report the need for dose adjustment to be made during pregnancy for women  
181 with bipolar disorder was highlighted [55], with dose escalation by up to an additional 350  
182 mg/daily in some cases to maintain symptom control during gestation. Further, previous  
183 reports of foetal exposure of quetiapine have occurred at dose ranges of 300-600 mg/day during  
184 gestation with no harmful effects on the new-born [56-59]. Interestingly a dose of 1200 mg/day  
185 was also used at mid-pregnancy (21 weeks gestation) as identified in a case report by Çabuk  
186 [60], which resulted in a normal birth. Although mainly case reports, these serve as useful  
187 guidance for potential dose escalation strategies required.

188

189 In order to assess the requirement for dose optimisation, simulations were conducted with 100  
190 subjects (10x10 design) aged 20-30 years. Simulations were commenced on day 1 of gestation  
191 and terminated on day 1 of week 39. Dose escalation studies included 'baseline' simulations  
192 of 200 mg twice daily and subsequently by 50 mg increments every 3 days to a maximum of  
193 700 mg twice daily. Data was sampled on the final 24 hour period of every 5<sup>th</sup> week up to and  
194 including week 38.

#### 195 **2.5 Predictive Performance**

196 For all simulations in steps 1-3, a prediction of a pharmacokinetic metric to within two-fold  
197 (0.5-2.0 fold) of published clinical data was generally accepted as part of the 'optimal'  
198 predictive performance [61-63].



## 199 2.7 Visual Predictive Checks

200 Model predictions in step 1-3 were compared to clinical studies using a visual predictive  
201 checking (VPC) strategy [64]. In this approach, the predicted mean/median and 5<sup>th</sup> and 95<sup>th</sup>  
202 percentiles of the concentration–time profiles (generated from Simcyp®) were compared  
203 against the observed data for any validation data sets. The prediction was assumed to be valid  
204 when the predicted data points overlapped with the observed data sets.

## 205 2.8 Data and statistical analysis

206 All observed data obtained from clinical studies were extracted using WebPlotDigitizer v.3.10  
207 (<http://arohatgi.info/WebPlotDigitizer/>). Statistical analysis was conducted using a non-  
208 parametric Kruskal-Wallis with a Dunn's multiple comparison post-hoc test. Statistical  
209 significance was confirmed where a  $P < 0.05$  was computed.

210

## 211 3. RESULTS

### 212 3.1 Step 1: Validation of quetiapine

213 A previously published quetiapine model was adapted with the incorporation of a full-PBPK  
214 model in order to predict tissue partition coefficient and enable a full mechanistic model to be  
215 utilised, in addition to the incorporation of a CYP3A5 metabolic pathway. The adapted file  
216 was validated against a range of published clinical studies using the Simcyp Healthy Volunteer  
217 population group (See section 2.1). For all single and multi-dose studies (Supplementary  
218 Materials: Section 2 Figure S1) along with drug-drug interactions simulations (Supplementary  
219 Materials: Section 2 Figure S2), the simulated plasma concentration-time profiles were  
220 successfully predicted to within the observed range for each study and model-predicted  $t_{\max}$ ,  
221  $C_{\max}$ , and AUC were predicted to within 2-fold of the reported parameters for each study,  
222 confirming successful validation (Table 1).

223

224 When compared to non-pregnant females (baseline), the median steady-state trough plasma  
225 concentrations of quetiapine decrease during gestation (Figure 1) with a statistically significant  
226 difference between baseline and the mid-point of trimesters 1-3 (final day of weeks 6, 20 and  
227 32 respectively) ( $P < 0.001$ , Dunn's post-hoc comparison) (Table 2). During gestation the  
228 predicted median plasma concentration decreased by between 52-58 %.

229 The reduced plasma concentration during gestation was associated with a concomitant increase  
230 in oral clearance (CL/F) which was significantly different from baseline from gestational week  
231 10 onwards ( $P < 0.05$ , Dunn's post-hoc comparison) and reached a maximum at GW 25, 204  
232 L/h  $\pm$  100.8 L/h compared to baseline, 121.9 L/h  $\pm$  51.8 L/h (Figure 2A). Further, changes in  
233 volume of distribution are significant from week 25 onwards, rising from a baseline of 329.2  
234 L  $\pm$  71 L to 368.4 L  $\pm$  71.3 L at GW 38 (Figure 2B). A statistically significant increase in  
235 unbound fraction was also noted from GW 10 onwards and with  $f_{u,plasma}$  being 21-26 % greater  
236 from weeks 30 onwards ( $f_{u,plasma} = 0.0218-0.0225$ ) (Figure 2C).

237 Understanding the importance of maternal physiological changes during gestation on  
238 quetiapine pharmacokinetics is clearly multifaceted. Therefore we conducted a sensitivity  
239 analysis using a non-pregnant and pregnant (GW: 10, 20 and 30) female population group  
240 where we directly examined the impact of variation in the CYP 3A4 hepatic abundance (137  
241 pmol/mg protein to 180 pmol/mg protein, representing a 30 % increase from baseline levels)  
242 and Kp scalar (1 to 3, representing a Vss range of 3.8 L/kg to 11 L/kg; implemented using  
243 Simcyp estimated Kp's) (Figure 3). When considering non-pregnant subjects, the trough serum  
244 concentrations are largely sensitive to changes in both Vss (Kp scalar) and CYP 3A4  
245 abundance, although the former has a greater influence. Conceptually, an increase in Vss  
246 would result in a net reduction in peak ( $C_{max}$ ) plasma concentrations with a concomitant shift  
247 in the distribution and elimination phases of the drug. However, this shift in the latter phases  
248 of the plasma concentration-time profile would result in a net increase in the trough plasma  
249 concentration ( $C_{min}$ ) (Figure 3A). At a fixed hepatic abundance, for example the default hepatic  
250 abundance in healthy (non-pregnant) subjects of 137 pmol/mg protein, any increase in Kp  
251 scalar (and hence increased in Vss) would increase the  $C_{min}$  (Figure 3B). However, during  
252 gestation the increase in CYP 3A4 hepatic abundance would negate the impact of an increase  
253 in Vss on the  $C_{min}$ , and result in a net reduction in trough plasma concentration (Figure 3).

254

#### 255 **3.4 Step 4: Dose adjustment during gestation**

256 In order to address the reduced plasma concentration during gestation, a dose escalation  
257 strategy was explored, whereby doses were increased by 50 mg increments every 3 days to a  
258 maximum of 500 mg twice daily, from a baseline dose of 200 mg twice daily.

259 As expected, the dose increase during gestation resulted in an increase in median plasma  
260 concentration (Figure 4). A dose increase of 300 mg (i.e. 500 mg twice daily) was required to

261 yield > 70 % of subjects with a trough plasma concentration in excess of 50 ng/mL throughout  
262 gestation (Table 3). However, a dose increase of 500 mg (i.e. 700 mg twice daily) was required  
263 to ensure >60 % of subjects possessed a trough plasma concentration in excess of 100 ng/mL  
264 throughout gestation (Table 3).

265

266

#### 267 **4. DISCUSSION**

268 The decision to use any pharmacological intervention during pregnancy is challenging  
269 for the mother in addition to the prescriber and requires clear knowledge of potential harmful  
270 effects on the developing foetus and risks such as the development of gestational diabetes.  
271 However, the choice to continue treatment or not, can be overshadowed by the clinical need  
272 for therapy during gestation, and the potential consequences of withdrawing treatment [13, 14].

273 Gestation brings about clear physiological changes which are known to alter the  
274 pharmacokinetic profile of drugs. However, the consequences of such changes are often  
275 difficult to ascertain clinically in a controlled trial for obvious ethical reasons. However, in an  
276 attempt to assess the potential impact of pregnancy on antipsychotic therapy, the use of robust  
277 mechanistic pharmacokinetic models allows for a prospective assessment of the potential  
278 impact and changes in plasma concentrations.

279 A recent report by Westin *et al* [28] examined the plasma concentrations of antipsychotics  
280 during gestation from retrospective analysis of therapeutic drug monitoring (TDM) clinical  
281 data from Norway. They identified that quetiapine and aripiprazole exhibited a significant  
282 decrease in plasma concentrations during gestation, by between 50-80 % by trimester 3.  
283 Further decrease were noted for perphenazine and haloperidol, but this was limited by the  
284 number of TDM measurements available. Nevertheless, the potential for gestation-related  
285 decrease in antipsychotic plasma concentrations was noted.

286

287 Given the lack of more detailed clinical studies examining these phenomena, this study applied  
288 the principle of pharmacokinetic modelling to prospectively assess the use of quetiapine in  
289 pregnancy population groups and attempted to relate changes in plasma concentrations during  
290 gestation to a potential therapeutic window region. The Simcyp Pregnancy PBPK model has  
291 been utilised by our group [65] and others [32, 33] for prediction of the impact of changes in

292 plasma concentrations associated with gestation, however this is the first time it has been  
293 utilised in the context of quetiapine.

294 The model developed incorporated adaptations to two existing quetiapine PBPK models [35,  
295 37] and was validated against single and multiple dose studies (Supplementary Materials:  
296 Section 2 Figure S2). The resulting predictions were within 2-fold of those reported along with  
297 appropriate VPC confirming population level variability in plasma concentrations were  
298 appropriately predicted in relation to the clinically reports variability. Further, the inclusion of  
299 the revisions to the CYP 3A5 component [37] were able to recapitulate the impact of  
300 appropriate DDIs on plasma concentrations (Supplementary Materials: Section 2 Figure S3).

301 To our knowledge, Westin *et al* [28] is the only publication (to date) containing quetiapine  
302 plasma concentrations throughout gestation and this was used as the basis for validating the  
303 quetiapine pregnancy PBPK model. Simulations were run for the entire gestation period (38  
304 weeks) with sampling of the first day on each week for every 5 weeks reported (Figure 1). For  
305 non-pregnant subjects (baseline), model predicted plasma concentrations ( $54.59 \text{ ng/mL} \pm 26.98$   
306  $\text{ng/mL}$ ) were within 2-fold of those reported by Westin *et al* [28] ( $75.6 \text{ ng/mL}$ ) (Table 2), whilst  
307 also spanning across a similar range. Westin *et al* [28] reported a 22 %, 57 % and 76 % decrease  
308 in mean plasma concentration at for trimesters 1, 2 and 3 respectively. Using the PBPK model  
309 we demonstrated a similar decrease of 52-58 % across gestation, although the predicted  
310 decrease for trimester 1 was greater than that reported [28]. Nonetheless, the trend throughout  
311 gestation for a decrease in plasma concentration was similar, and represents an important  
312 phenomenon, which is likely to result in sub-therapeutic plasma concentrations if we assume a  
313 lower limit of the therapeutic window to be  $100 \text{ ng/mL}$ .

314 In order to identify the cause of this change in plasma concentrations during gestation, we first  
315 examined the impact of changes in CYP 3A4 expression on oral clearance. Previous reports  
316 have identified significant alterations in CYP 3A4 expression with gestation, and given the  
317 major contribution of CYP 3A4 to overall CYP-mediated metabolic clearance,  $> 90 \%$  [18, 40],  
318 this is a key component for the overall pharmacokinetics of quetiapine. The impact of gestation  
319 on the metabolic clearance of CYP 3A4 substrates has been previously reported as leading to  
320 an approximate 25-40 % increase in the clearance [22, 66]

321 An increase in oral clearance was observed at week 5 for pregnant subjects, ( $149.5 \text{ L/h} \pm 75.17$   
322  $\text{L/h}$ ) compared to baseline (non-pregnant) subjects at the same time point ( $121.9 \text{ L/h} \pm 51.53$   
323  $\text{L/h}$ ) (Figure 2A), however this was not statistically significant. From week 10 to 38, the oral

324 clearance increased, compared to baseline subjects, with week 20 demonstrating the greatest  
325 difference ( $184.1 \text{ L/h} \pm 100.5 \text{ L/h}$ ) ( $P < 0.001$ ) (Figure 2A). Further, an increase in total body  
326 water and plasma volume that occur throughout gestation did not have a significant impact on  
327 the  $V_{ss}$  until week 25, where  $V_{ss}$  reached  $357.2 \text{ L} \pm 71.9 \text{ L}$ , compared to  $329.2 \text{ L} \pm 71 \text{ L}$  for  
328 non-pregnant subjects (Figure 2B). Previous reports have demonstrated  $V_{ss}$  can range from  
329 400-800 L for non-pregnant subjects, for both single and multidose studies [67-69]. The  
330 approximate 10 % increase in  $V_{ss}$  during gestation, although significant, may only contribute  
331 a minor role to the change in trough concentration. A net increase in the unbound fraction  
332 plasma ( $f_{u,plasma}$ ) (21-26 % greater from weeks 30 onwards) was also simulated when comparing  
333 baseline (Figure 2C). This net increase would result in an increase in circulating unbound drug,  
334 resulting in an increase in the volume of distribution whilst also partly contributing to  
335 potentially enhanced exposure of drug to the liver. However, the conceptualisation of this  
336 effect on trough levels is multifaceted. The gestation-mediated increase in CYP 3A4 hepatic  
337 abundance negates the impact of an increase in the volume of distribution and results in a net  
338 reduction in trough plasma concentration (Figure 3).

339 To address the reduction in quetiapine plasma concentrations during gestation, we assessed the  
340 impact of dose escalation which was required to recapitulate trough plasma concentrations to  
341 within the therapeutic window. Because of the uncertainty surrounding the precise range of  
342 the therapeutic window, a lower limit was set at either 50 ng/mL or 100 ng/mL (see section  
343 2.4). In non-pregnant subjects, a 200 mg twice daily dose yielded a median steady-state trough  
344 concentration of  $59.47 \text{ ng/mL} \pm 26.98 \text{ ng/mL}$ , which significantly decreased during gestation  
345 to a minimum of 30.55 ng/mL at GW 20 ( $P < 0.001$ , Dunn's post-hoc comparison) (Figure 4)  
346 (Supplementary Materials: Section 3 Table S2). Further, this resulted in a significant number  
347 of subjects failing to attain the lower therapeutic window, < 35 % of subjects for 50 ng/mL  
348 (Table 4) and < 15 % of subjects for 100 ng/mL (Table 3). This trend broadly concurs with  
349 those reported by Westin *et al* [28], where the majority of reported plasma concentrations  
350 during gestation fell below the 50 ng/mL lower limit (Figure 1), highlighting the need to  
351 consider dose escalation during gestation.

352 Although a dose increase to 500 mg twice daily would be sufficient to ensure 30-50 % of  
353 subjects attained the upper therapeutic window of 100 ng/mL (Table 3), a dose increase to 700  
354 mg twice daily was identified as satisfying the requirement to attain both the 50 ng/mL and 100  
355 ng/mL lower windows (Figure 4), with attainment of > 95 % and > 62 % of subjects  
356 respectively. Whilst trials have suggested an upper dose of 800 mg/day [2, 70, 71], higher

357 doses of between 800-2000 mg/day [72-76] have been reported to be tolerated in acute and  
358 maintenance therapy. Further, sparse case reports are available of significantly higher  
359 overdoses of least 20-24 g being ingested with little acute effects [77, 78].

360 The increase in dose may warrant closer monitoring with possible monthly clinical evaluations  
361 during gestation. This would allow for assessment for any worsening of mood disorder  
362 symptoms during administration of higher doses of quetiapine. This can consist of trained  
363 clinician administered structured interviews (e.g. SIGH-ADS[79] or MRS[80]). Furthermore,  
364 recommendations from the Royal College of Psychiatrists Consensus Statement [81] advocated  
365 the use of scales such as the Brief Psychiatric Rating Scale (BPRS)[82] and Health of the  
366 Nation Outcome Scales (HoNOS)[83] in addition to assessing adverse effects through the  
367 Liverpool University Neuroleptic Side Effect Rating Scale (LUNSERS)[84], for high dose  
368 antipsychotic use.

369 Given that the metabolic clearance of quetiapine is mediated largely by CYP3A4 [18], and  
370 gestation can result in a significant increase in the expression of CYP3A4 [19-21], an increase  
371 in dose would be necessary during gestation to ensure trough plasma concentrations are in  
372 excess of the lower therapeutic window.

373 Although limited studies have examined the need for a dose increase during pregnancy, those  
374 that have reported this have shown that a 2-to-3 fold increase in dose is required in many cases  
375 [60, 85, 86], dose increase were required in 80 % of the patients studied during pregnancy.

## 376 5. CONCLUSIONS

377 The primary outcome of our work is that quetiapine doses as high as 1400 mg/day may be  
378 required during gestation, which is supported by case reports and clinical studies demonstrating  
379 few adverse clinical effects when using at doses of in excess of 800 mg/day.

380 For the first time, through the implementation of virtual clinical trials analysis, we have  
381 demonstrated that the reduction in quetiapine plasma concentrations are driven by both  
382 alterations in tissue physiology and the impact this has on the overall  $V_{ss}$ , in addition to  
383 variation in CYP 3A4 abundance changes during gestation. However, for other antipsychotics,  
384 this phenomenon would largely depend upon the gestational changes in specific CYP isozymes.  
385 For example, clozapine metabolic clearance is primarily mediated by CYP 1A2, which itself  
386 can undergo significant decreases in pregnancy.

387 Further studies are required to assess both the extent of this gestational change on plasma  
388 concentrations but also to also better identify a potential therapeutic range to better optimise  
389 any necessary dose adjustments. However, we believe this study will provide a pragmatic basis  
390 with which to consider dose adjustment throughout gestation.

391

392

### 393 CONFLICTS OF INTEREST

394 The authors declare that they have no conflicts of interest.

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398

### 399 REFERENCES

400

401 1. Peuskens, J. and C.G. Link, *A comparison of quetiapine and chlorpromazine in the*  
402 *treatment of schizophrenia*. *Acta Psychiatr Scand*, 1997. **96**(4): p. 265-73.

403 2. Arvanitis, L.A. and B.G. Miller, *Multiple fixed doses of "Seroquel" (quetiapine) in*  
404 *patients with acute exacerbation of schizophrenia: a comparison with haloperidol and*  
405 *placebo*. *The Seroquel Trial 13 Study Group*. *Biol Psychiatry*, 1997. **42**(4): p. 233-46.

406 3. Hanley, G.E. and B. Mintzes, *Patterns of psychotropic medicine use in pregnancy in*  
407 *the United States from 2006 to 2011 among women with private insurance*. *BMC*  
408 *pregnancy and childbirth*, 2014. **14**(1): p. 242.

409 4. Kennedy, D., et al., *Review of calls to an Australian teratogen information service*  
410 *regarding psychotropic medications over a 12-year period*. *Australian and New*  
411 *Zealand Journal of Obstetrics and Gynaecology*, 2013. **53**(6): p. 544-552.

412 5. Ennis, Z.N. and P. Damkier, *Pregnancy exposure to olanzapine, quetiapine,*  
413 *risperidone, aripiprazole and risk of congenital malformations. A systematic review*.  
414 *Basic & clinical pharmacology & toxicology*, 2015. **116**(4): p. 315-320.

415 6. Small, J.G., et al., *Quetiapine in patients with schizophrenia. A high- and low-dose*  
416 *double-blind comparison with placebo*. *Seroquel Study Group*. *Arch Gen Psychiatry*,  
417 1997. **54**(6): p. 549-57.

- 418 7. Chisolm, M.S. and J.L. Payne, *Management of psychotropic drugs during pregnancy*.  
419 *Bmj*, 2016. **532**: p. h5918.
- 420 8. Andersson, L., et al., *Point prevalence of psychiatric disorders during the second*  
421 *trimester of pregnancy: a population-based study*. *Am J Obstet Gynecol*, 2003. **189**(1):  
422 p. 148-54.
- 423 9. Marcus, S.M., et al., *Depressive symptoms among pregnant women screened in*  
424 *obstetrics settings*. *J Womens Health (Larchmt)*, 2003. **12**(4): p. 373-80.
- 425 10. Viguera, A.C., et al., *Risk of recurrence in women with bipolar disorder during*  
426 *pregnancy: prospective study of mood stabilizer discontinuation*. *Am J Psychiatry*,  
427 2007. **164**(12): p. 1817-24; quiz 1923.
- 428 11. Gilbert, P.L., et al., *Neuroleptic withdrawal in schizophrenic patients. A review of the*  
429 *literature*. *Arch Gen Psychiatry*, 1995. **52**(3): p. 173-88.
- 430 12. Baldessarini, R.J. and A.C. Viguera, *Neuroleptic withdrawal in schizophrenic patients*.  
431 *Arch Gen Psychiatry*, 1995. **52**(3): p. 189-92.
- 432 13. National Institute for Health and Care Excellence. *Antenatal and postnatal mental*  
433 *health: clinical management and service guidance (Clinical guideline [CG192])*. 2018  
434 [cited 2019 May]; Available from: [https://www.nice.org.uk/guidance/cg192/chapter/1-](https://www.nice.org.uk/guidance/cg192/chapter/1-Recommendations)  
435 [Recommendations](https://www.nice.org.uk/guidance/cg192/chapter/1-Recommendations).
- 436 14. McAllister-Williams, R.H., et al., *British Association for Psychopharmacology*  
437 *consensus guidance on the use of psychotropic medication preconception, in pregnancy*  
438 *and postpartum 2017*. *Journal of Psychopharmacology*, 2017. **31**(5): p. 519-552.
- 439 15. Kim, J.J. and R.K. Silver, *Perinatal suicide associated with depression diagnosis and*  
440 *absence of active treatment in 15-year UK national inquiry*. *Evid Based Ment Health*,  
441 2016. **19**(4): p. 122.
- 442 16. Huybrechts, K.F., et al., *Antipsychotic Use in Pregnancy and the Risk for Congenital*  
443 *Malformations*. *JAMA Psychiatry*, 2016. **73**(9): p. 938-46.
- 444 17. Cohen, L.S., et al., *Reproductive Safety of Second-Generation Antipsychotics: Current*  
445 *Data From the Massachusetts General Hospital National Pregnancy Registry for*  
446 *Atypical Antipsychotics*. *Am J Psychiatry*, 2016. **173**(3): p. 263-70.
- 447 18. Grimm, S.W., K.R. Stams, and K. Bui, *In vitro prediction of potential metabolic drug*  
448 *interactions for Seroquel*. *Schizophrenia Research*, 1997. **24**(1): p. 198.
- 449 19. Hebert, M.F., et al., *Effects of pregnancy on CYP3A and P-glycoprotein activities as*  
450 *measured by disposition of midazolam and digoxin: a University of Washington*  
451 *specialized center of research study*. *Clin Pharmacol Ther*, 2008. **84**(2): p. 248-53.



- 452 20. Hodge, L.S. and T.S. Tracy, *Alterations in drug disposition during pregnancy: implications for drug therapy*. *Expert Opin Drug Metab Toxicol*, 2007. **3**(4): p. 557-71.  
453
- 454 21. Hirt, D., et al., *Pregnancy-related effects on nelfinavir-M8 pharmacokinetics: a population study with 133 women*. *Antimicrobial agents and chemotherapy*, 2006.  
455 **50**(6): p. 2079-2086.  
456
- 457 22. Tracy, T.S., et al., *Temporal changes in drug metabolism (CYP1A2, CYP2D6 and CYP3A Activity) during pregnancy*. *Am J Obstet Gynecol*, 2005. **192**(2): p. 633-9.  
458
- 459 23. Qasqas, S.A., et al., *Cardiovascular pharmacotherapeutic considerations during pregnancy and lactation*. *Cardiol Rev*, 2004. **12**(4): p. 201-21.  
460
- 461 24. Pirani, B.B., D.M. Campbell, and I. MacGillivray, *Plasma volume in normal first pregnancy*. *J Obstet Gynaecol Br Commonw*, 1973. **80**(10): p. 884-7.  
462
- 463 25. Murphy, M.M., et al., *The pregnancy-related decrease in fasting plasma homocysteine is not explained by folic acid supplementation, hemodilution, or a decrease in albumin in a longitudinal study*. *Am J Clin Nutr*, 2002. **76**(3): p. 614-9.  
464  
465
- 466 26. Hayashi, M., et al., *Changes in urinary excretion of six biochemical parameters in normotensive pregnancy and preeclampsia*. *Am J Kidney Dis*, 2002. **39**(2): p. 392-400.  
467
- 468 27. Cheung, C.K., T. Lao, and R. Swaminathan, *Urinary excretion of some proteins and enzymes during normal pregnancy*. *Clin Chem*, 1989. **35**(9): p. 1978-80.  
469
- 470 28. Westin, A.A., et al., *Treatment With Antipsychotics in Pregnancy: Changes in Drug Disposition*. *Clinical pharmacology and therapeutics*, 2018. **103**(3): p. 477-484.  
471
- 472 29. Baer, G.R., et al., *Addendum to OSE Safety Review of Seroquel®*, O.o.P. Therapeutics, Editor. 2016, Food and Drug Administration: Maryland, USA.  
473
- 474 30. Bateman, D.N., et al., *TOXBASE: poisons information on the internet*. *Emerg Med J*, 2002. **19**(1): p. 31-4.  
475
- 476 31. Abduljalil, K., et al., *Anatomical, physiological and metabolic changes with gestational age during normal pregnancy: a database for parameters required in physiologically based pharmacokinetic modelling*. *Clin Pharmacokinet*, 2012. **51**(6): p. 365-96.  
477  
478
- 479 32. Gaohua, L., et al., *A pregnancy physiologically based pharmacokinetic (p-PBPK) model for disposition of drugs metabolized by CYP1A2, CYP2D6 and CYP3A4*. *Br J Clin Pharmacol*, 2012. **74**(5): p. 873-85.  
480  
481
- 482 33. Jogiraju, V.K., et al., *Application of physiologically based pharmacokinetic modeling to predict drug disposition in pregnant populations*. *Biopharm Drug Dispos*, 2017. **38**(7): p. 426-438.  
483  
484

- 485 34. Lu, G., et al., *Physiologically-based pharmacokinetic (PBPK) models for assessing the*  
486 *kinetics of xenobiotics during pregnancy: achievements and shortcomings.* *Curr Drug*  
487 *Metab*, 2012. **13**(6): p. 695-720.
- 488 35. Johnson, T.N., D. Zhou, and K.H. Bui, *Development of physiologically based*  
489 *pharmacokinetic model to evaluate the relative systemic exposure to quetiapine after*  
490 *administration of IR and XR formulations to adults, children and adolescents.*  
491 *Biopharm Drug Dispos*, 2014. **35**(6): p. 341-52.
- 492 36. Bakken, G.V., et al., *Metabolism of quetiapine by CYP3A4 and CYP3A5 in presence or*  
493 *absence of cytochrome B5.* *Drug Metab Dispos*, 2009. **37**(2): p. 254-8.
- 494 37. Alqahtani, S. and A. Kaddoumi, *Development of a Physiologically Based*  
495 *Pharmacokinetic/Pharmacodynamic Model to Predict the Impact of Genetic*  
496 *Polymorphisms on the Pharmacokinetics and Pharmacodynamics Represented by*  
497 *Receptor/Transporter Occupancy of Central Nervous System Drugs.* *Clin*  
498 *Pharmacokinet*, 2016. **55**(8): p. 957-69.
- 499 38. Rodgers, T., D. Leahy, and M. Rowland, *Physiologically based pharmacokinetic*  
500 *modeling I: predicting the tissue distribution of moderate-to-strong bases.* *J Pharm Sci*,  
501 2005. **94**(6): p. 1259-76.
- 502 39. Rodgers, T. and M. Rowland, *Physiologically based pharmacokinetic modelling 2:*  
503 *predicting the tissue distribution of acids, very weak bases, neutrals and zwitterions.* *J*  
504 *Pharm Sci*, 2006. **95**(6): p. 1238-57.
- 505 40. Grimm, S.W., et al., *Effects of cytochrome P450 3A modulators ketoconazole and*  
506 *carbamazepine on quetiapine pharmacokinetics.* *British Journal of Clinical*  
507 *Pharmacology*, 2006. **61**(1): p. 58-69.
- 508 41. Wong, Y.W., C. Yeh, and P.T. Thyrum, *The effects of concomitant phenytoin*  
509 *administration on the steady-state pharmacokinetics of quetiapine.* *J Clin*  
510 *Psychopharmacol*, 2001. **21**(1): p. 89-93.
- 511 42. Potkin, S.G., et al., *Effect of fluoxetine and imipramine on the pharmacokinetics and*  
512 *tolerability of the antipsychotic quetiapine.* *J Clin Psychopharmacol*, 2002. **22**(2): p.  
513 174-82.
- 514 43. WHO Collaborative Centre for Drug Statistics Methodology. *ATC/DDD Index 2016*  
515 2016 [cited 2018 November]; Available from: [https://www.whocc.no/atc\\_ddd\\_index/](https://www.whocc.no/atc_ddd_index/).
- 516 44. Mauri, M.C., et al., *Clinical Pharmacokinetics of Atypical Antipsychotics: An Update.*  
517 *Clin Pharmacokinet*, 2018.
- 518 45. Hiemke, C., et al., *Consensus Guidelines for Therapeutic Drug Monitoring in*  
519 *Neuropsychopharmacology: Update 2017.* *Pharmacopsychiatry*, 2018. **51**(1-02): p. 9-  
520 62.

- 521 46. Castberg, I., E. Skogvoll, and O. Spigset, *Quetiapine and drug interactions: evidence*  
522 *from a routine therapeutic drug monitoring service.* J Clin Psychiatry, 2007. **68**(10): p.  
523 1540-5.
- 524 47. McConville, B.J., et al., *Pharmacokinetics, tolerability, and clinical effectiveness of*  
525 *quetiapine fumarate: an open-label trial in adolescents with psychotic disorders.* The  
526 Journal of clinical psychiatry, 2000. **61**(4): p. 252-260.
- 527 48. Winter, H.R., et al., *Steady-state pharmacokinetic, safety, and tolerability profiles of*  
528 *quetiapine, norquetiapine, and other quetiapine metabolites in pediatric and adult*  
529 *patients with psychotic disorders.* J Child Adolesc Psychopharmacol, 2008. **18**(1): p.  
530 81-98.
- 531 49. Hasselstrom, J. and K. Linnet, *Quetiapine serum concentrations in psychiatric patients:*  
532 *the influence of comedication.* Ther Drug Monit, 2004. **26**(5): p. 486-91.
- 533 50. Sparshatt, A., et al., *Relationship between daily dose, plasma concentrations, dopamine*  
534 *receptor occupancy, and clinical response to quetiapine: a review.* J Clin Psychiatry,  
535 2011. **72**(8): p. 1108-23.
- 536 51. Kane, J.M., et al., *The expert consensus guideline series. Optimizing pharmacologic*  
537 *treatment of psychotic disorders. Introduction: methods, commentary, and summary.* J  
538 Clin Psychiatry, 2003. **64 Suppl 12**: p. 5-19.
- 539 52. Boggs, D.L., et al., *Quetiapine at high doses for the treatment of refractory*  
540 *schizophrenia.* Schizophrenia research, 2008. **101**(1-3): p. 347-348.
- 541 53. Lindenmayer, J.P., et al., *A randomized, double-blind, parallel-group, fixed-dose,*  
542 *clinical trial of quetiapine at 600 versus 1200 mg/d for patients with treatment-resistant*  
543 *schizophrenia or schizoaffective disorder.* J Clin Psychopharmacol, 2011. **31**(2): p.  
544 160-8.
- 545 54. Honer, W.G., et al., *A randomized, double-blind, placebo-controlled study of the safety*  
546 *and tolerability of high-dose quetiapine in patients with persistent symptoms of*  
547 *schizophrenia or schizoaffective disorder.* J Clin Psychiatry, 2012. **73**(1): p. 13-20.
- 548 55. Pinheiro, E.A., K.L. Wisner, and C.T. Clark, *Quetiapine Dose Adjustments in Pregnant*  
549 *and Postpartum Women With Bipolar Disorder.* J Clin Psychopharmacol, 2018. **38**(1):  
550 p. 89-91.
- 551 56. Gentile, S., *Quetiapine-fluvoxamine combination during pregnancy and while*  
552 *breastfeeding.* Arch Womens Ment Health, 2006. **9**(3): p. 158-9.
- 553 57. Yaris, F., et al., *Use of polypharmacotherapy in pregnancy: a prospective outcome in*  
554 *a case.* Prog Neuropsychopharmacol Biol Psychiatry, 2004. **28**(3): p. 603-5.

- 555 58. Taylor, T.M., et al., *Safety of quetiapine during pregnancy*. Am J Psychiatry, 2003.  
556 **160**(3): p. 588-9.
- 557 59. Tenyi, T., M. Trixler, and Z. Keresztes, *Quetiapine and pregnancy*. Am J Psychiatry,  
558 2002. **159**(4): p. 674.
- 559 60. Cabuk, D., et al., *Quetiapine use for the treatment of manic episode during pregnancy*.  
560 Arch Womens Ment Health, 2007. **10**(5): p. 235-6.
- 561 61. Edginton, A.N., W. Schmitt, and S. Willmann, *Development and evaluation of a  
562 generic physiologically based pharmacokinetic model for children*. Clin  
563 Pharmacokinet, 2006. **45**(10): p. 1013-34.
- 564 62. Ginsberg, G., et al., *Physiologically based pharmacokinetic (PBPK) modeling of  
565 caffeine and theophylline in neonates and adults: implications for assessing children's  
566 risks from environmental agents*. J Toxicol Environ Health A, 2004. **67**(4): p. 297-329.
- 567 63. Parrott, N., et al., *Development of a physiologically based model for oseltamivir and  
568 simulation of pharmacokinetics in neonates and infants*. Clin Pharmacokinet, 2011.  
569 **50**(9): p. 613-23.
- 570 64. U.S. Food and Drug Administration. *Summary Minutes of the Advisory Committee for  
571 Pharmaceutical Science and Clinical Pharmacology*. 2012 [cited 2018 29th May];  
572 Available from: [https://wayback.archive-  
573 it.org/7993/20170403224110/https://www.fda.gov/AdvisoryCommittees/Committees  
574 MeetingMaterials/Drugs/AdvisoryCommitteeForPharmaceuticalScienceandClinicalPh  
575 armacology/ucm286697.htm](https://wayback.archive-it.org/7993/20170403224110/https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AdvisoryCommitteeForPharmaceuticalScienceandClinicalPharmacology/ucm286697.htm).
- 576 65. Olafuyi, O. and R.K.S. Badhan, *Dose Optimization of Chloroquine by Pharmacokinetic  
577 Modeling During Pregnancy for the Treatment of Zika Virus Infection*. J Pharm Sci,  
578 2019. **108**(1): p. 661-673.
- 579 66. Villani, P., et al., *Pharmacokinetics of nelfinavir in HIV-1-infected pregnant and  
580 nonpregnant women*. Br J Clin Pharmacol, 2006. **62**(3): p. 309-15.
- 581 67. Thyrum, P.T., Y.W. Wong, and C. Yeh, *Single-dose pharmacokinetics of quetiapine in  
582 subjects with renal or hepatic impairment*. Prog Neuropsychopharmacol Biol  
583 Psychiatry, 2000. **24**(4): p. 521-33.
- 584 68. DeVane CL, M.J., *Drugs as substrates of metabolic enzymes: antipsychotics.*, T.K.  
585 Levy RH, Trager WF, Hansten PD, Eichelbaum M., Editor. 2000, Lippincott-Raven  
586 Press: Baltimore (MD).
- 587 69. Gefvert, O., et al., *Time course of central nervous dopamine-D2 and 5-HT2 receptor  
588 blockade and plasma drug concentrations after discontinuation of quetiapine  
589 (Seroquel) in patients with schizophrenia*. Psychopharmacology (Berl), 1998. **135**(2):  
590 p. 119-26.

- 591 70. Purdon, S.E., et al., *Neuropsychological change in patients with schizophrenia after*  
592 *treatment with quetiapine or haloperidol*. J Psychiatry Neurosci, 2001. **26**(2): p. 137-  
593 49.
- 594 71. Copolov, D.L., C.G. Link, and B. Kowalczyk, *A multicentre, double-blind, randomized*  
595 *comparison of quetiapine (ICI 204,636, 'Seroquel') and haloperidol in schizophrenia*.  
596 Psychol Med, 2000. **30**(1): p. 95-105.
- 597 72. Nagy, J., *Efficacy, safety and tolerability of quetiapine: short-term high doses with*  
598 *long-term follow-up*. Int J Psychiatry Clin Pract, 2005. **9**(1): p. 16-21.
- 599 73. Pierre, J.M., et al., *High-dose quetiapine in treatment refractory schizophrenia*.  
600 Schizophr Res, 2005. **73**(2-3): p. 373-5.
- 601 74. Cornelis, C., et al., *A case of dose escalation of quetiapine in persistent insomnia*  
602 *disorder*. Acta Clin Belg, 2017. **72**(5): p. 346-348.
- 603 75. Khazaal, Y., et al., *Use of high doses of quetiapine in bipolar disorder episodes are not*  
604 *linked to high activity of cytochrome P4503A4 and/or cytochrome P4502D6*. Psychiatr  
605 Q, 2013. **84**(3): p. 329-35.
- 606 76. Khazaal, Y., et al., *Quetiapine dosage in bipolar disorder episodes and mixed states*.  
607 Prog Neuropsychopharmacol Biol Psychiatry, 2007. **31**(3): p. 727-30.
- 608 77. Balit, C.R., et al., *Quetiapine poisoning: a case series*. Ann Emerg Med, 2003. **42**(6):  
609 p. 751-8.
- 610 78. Harmon, T.J., et al., *Loss of consciousness from acute quetiapine overdose*. J Toxicol  
611 Clin Toxicol, 1998. **36**(6): p. 599-602.
- 612 79. Williams, J. and M. Terman, *Structured interview guide for the Hamilton depression*  
613 *rating scale with atypical depression supplement (SIGH-ADS)*. New York: New York  
614 State Psychiatric Institute, 2003.
- 615 80. Endicott, J. and R.L. Spitzer, *A diagnostic interview: the schedule for affective*  
616 *disorders and schizophrenia*. Archives of general psychiatry, 1978. **35**(7): p. 837-844.
- 617 81. Psychiatrists, R.C.o., *Consensus statement on high-dose antipsychotic medication*.  
618 CR190 ed. 2014: Royal College of Psychiatrists.
- 619 82. Overall, J.E. and D.R. Gorham, *The Brief Psychiatric Rating Scale*. Psychological  
620 Reports, 1962. **10**(3): p. 799-812.
- 621 83. Wing, J., et al., *Health of the Nation Outcome Scales (HoNOS): research and*  
622 *development*. The British Journal of Psychiatry, 1998. **172**(1): p. 11-18.

- 623 84. Day, J.C., et al., *A self-rating scale for measuring neuroleptic side-effects. Validation*  
624 *in a group of schizophrenic patients.* Br J Psychiatry, 1995. **166**(5): p. 650-3.
- 625 85. Pinheiro, E.A., K.L. Wisner, and C.T. Clark, *Quetiapine Dose Adjustments in Pregnant*  
626 *and Postpartum Women With Bipolar Disorder.* Journal of clinical  
627 psychopharmacology, 2018. **38**(1): p. 89-91.
- 628 86. Uguz, F., *Prophylactic use of olanzapine and quetiapine from pregnancy to the*  
629 *postpartum period in women with bipolar disorder: a case series.* J Matern Fetal  
630 Neonatal Med, 2017. **30**(21): p. 2569-2571.

632 **Table 1: Summary pharmacokinetics parameters for validation studies in non-pregnant subjects**

633

634	<b>Study</b>	<b>Sampling day</b>	<b>C<sub>max</sub> (ng/mL)</b>	<b>t<sub>max</sub> (h)</b>	<b>AUC (ng/mL.h)<sup>a</sup></b>		
635	Grimm[40]	<b>Day 1</b>	Predicted	42.53 (25.32)	1 (0.23)	144.29 (97.29)	
636			Observed	45	1.25	181	
637		<b>Day 6</b> <b>+Ketoconazole</b>	Predicted	123.02 (27.76)	1.28 (0.29)	1002.99 (409.18)	
638			Observed	150	1.25	1123	
639		<b>Day 9</b>	Predicted	663.42 (405.11)	1 (0.23)	2784.12 (2317)	
640			Observed	1042	1.5	4650	
641		<b>Day 34</b> <b>+Carbamazepine</b>	Predicted	320.61 (131.19)	0.93 (0.22)	1137 (650.54)	
642			Observed	205	1.3	621	
643		Wong[41]	<b>Day 8</b>	Predicted	765.48 (339.7)	1 (0.22)	3168.82 (1673.07)
644				Observed	1048 (363)	1.4 (0.5)	3642 91375)
645			<b>Day 8</b> <b>+Phenytoin</b>	Predicted	439.01 (267.12)	0.94 (0.21)	1414.03 (1167.38)
646				Observed	359 (328)	1.13 (0.36)	728 (445)
647	Potkin [42]	<b>Day 21</b>	Predicted	1032.71(50)	0.98 (0.65-1.40)	4223.86 (61)	
			Observed	1124.6 (31.9)	1.23 (0.5-3)	4508.9 (39.8)	

647 Data represents mean (Standard deviation). <sup>a</sup> Calculated for current dosing period.

648 **Table 2: Trough plasma quetiapine concentration during pregnancy**

	<b>Baseline</b>	<b>T1</b>	<b>T2</b>	<b>T3</b>
	<sup>a</sup>			
	<b>(ng/mL)</b>			
Median	59.47	28.07	24.94	26.43
Mean	54.59	39.12	34.66	36.74
SD	26.98	29.09	25.26	26.41
SEM	4.61	6.20	5.38	5.63
CI high	47.71	46.82	41.39	44.18
CI low	31.09	22.16	19.96	21.23
Change (%) <sup>b</sup>		52.81	58.06	55.53

649

650 T1-T3 refers to each trimester; Data calculated from mid-point of each trimester; CI:  
 651 confidence interval; SD: Standard deviation; SEM: standard error of the mean. <sup>a</sup> Baseline  
 652 represents non-pregnant females; <sup>b</sup> Change refers to % changes from baseline.

653

654

655

656 **Table 3: Percentage of subjects with quetiapine trough concentrations greater than 50**  
 657 **and 100 ng/mL**

<b>Week</b>	<b>Dose Adjustment (mg)</b>							
	<b>50 ng/mL lower limit</b>				<b>100 ng/mL lower limit</b>			
	<b>Baseline</b>	<b>100</b>	<b>300</b>	<b>500</b>	<b>Baseline</b>	<b>100</b>	<b>300</b>	<b>500</b>
<b>5</b>	34	66	86	98	14	24	55	81
<b>10</b>	28	58	82	97	9	21	43	73
<b>15</b>	25	48	75	96	6	19	34	69
<b>20</b>	24	45	72	95	4	18	33	65
<b>25</b>	24	44	72	95	4	16	32	63
<b>30</b>	24	45	74	95	4	18	33	62
<b>35</b>	28	54	81	96	9	20	38	68
<b>38</b>	31	60	83	96	12	22	44	69

658 Data calculated from day 1 of each week; Baseline represents non-pregnant females.

659



660 **LIST OF FIGURES**

661

662 **Figure 1: Simulated quetiapine plasma concentrations during gestation**

663 Simulated quetiapine plasma concentrations were generated during gestation using the Simcyp  
664 Pregnancy population group, with the population group (n=33) redefined on a daily basis to  
665 update study group physiology during gestation. Simulated concentrations represent post-dose  
666 (trough concentrations) sampled 10 hours after dosing. Subjects were administered a 200 mg  
667 twice daily dose (dose escalated from 25 mg twice daily over 1 week). 'Baseline' refers to  
668 non-pregnant females. Simulated concentrations represent post-dose (trough concentrations)  
669 sampled 10 hours after dosing and collated at 5-week intervals over the gestation period. Red  
670 open circles represent observed (pooled) plasma concentrations obtained from a total of 33  
671 subjects. Black open circles present simulated plasma concentrations.

672

673 **Figure 2: Impact of physiological alterations during pregnancy on quetiapine**  
674 **pharmacokinetics**

675 Changes in quetiapine (A) clearance, (B) volume of distribution and (C) unbound fraction in  
676 plasma at baseline (non-pregnant females) and during gestation. Gestational week is indicated  
677 by GW. Box-plots ideates range (upper and lower bars) with calculation of median and 25<sup>th</sup>/75<sup>th</sup>  
678 percentiles. \* P < 0.05; \*\* P < 0.01; \*\*\* P < 0.001; \*\*\*\* P < 0.0001.

679

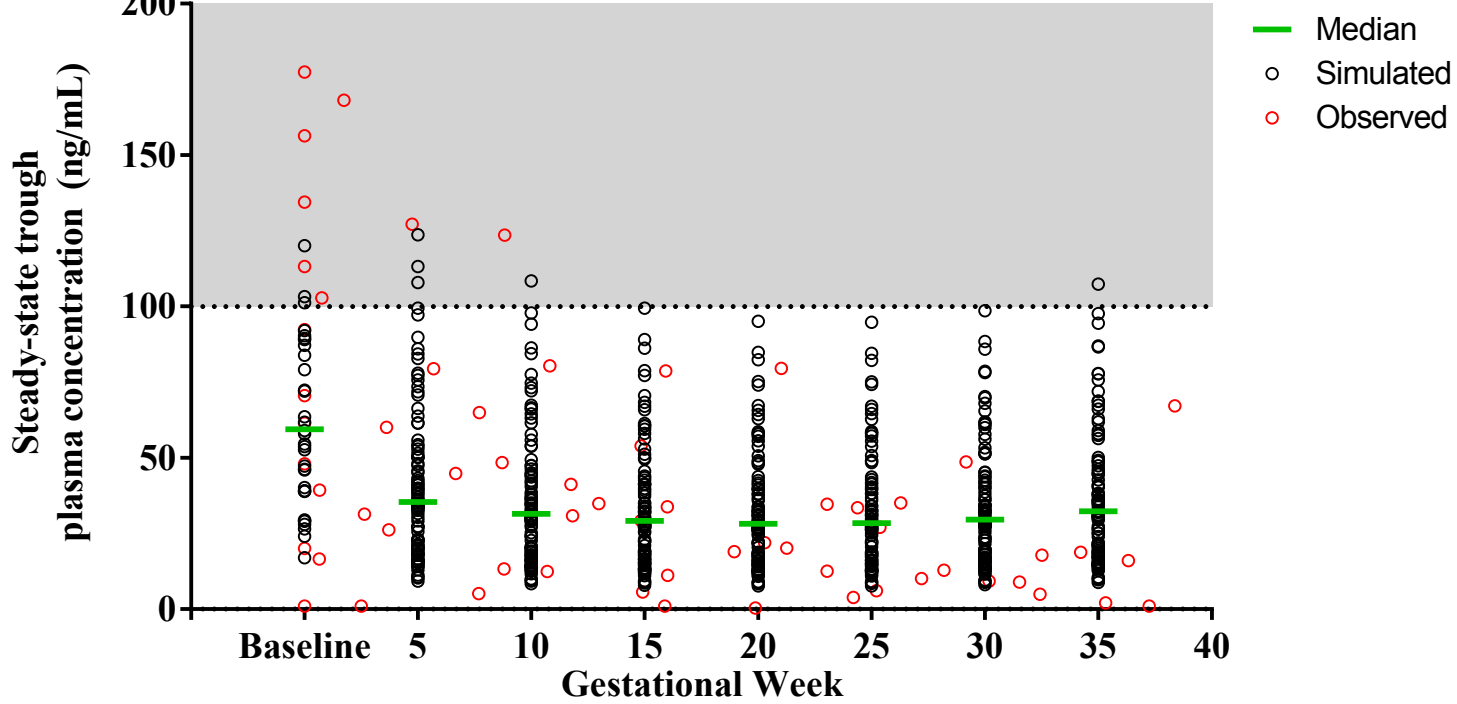
680 **Figure 3: Impact of alterations in Kp and CYP 3A4 abundance during pregnancy on**  
681 **quetiapine plasma concentrations**

682 (A) The impact of changes in Kp scalar and CYP 3A4 hepatic abundance on quetiapine  
683 plasma concentrations following multiple 200 mg oral doses (12-hourly). Solid lines  
684 represent fixed CYP 3A4 abundance but increasing Kp scalar, with dashed lines representing  
685 changes in Kp scalar but fixed CYP 3A4 abundance. (B) A sensitivity analysis comparing  
686 the impact of variation in Kp scalar (1 to 3) and CYP 3A4 abundance (137 to 180 pmol/mg  
687 protein) on final dose trough plasma concentrations in non-pregnant (red) and GW10 to 30.

688

689 **Figure 4: Dose optimisation of quetiapine during gestation**

690 The impact of dose escalation on median quetiapine plasma concentrations during gestation.  
691 Box-plots indicate range (upper and lower bars) with calculation of median and 25<sup>th</sup>/75<sup>th</sup>  
692 percentiles. Baseline dose was 200 mg twice daily with escalation indicated as the additive  
693 increase in dose from baseline. Dark shaded region indicates the proposed therapeutic  
694 window (100-500 ng/mL) with the lighter shaded region (50-100 ng/mL) indicating the  
695 proposed 'extended' range of the therapeutic window.



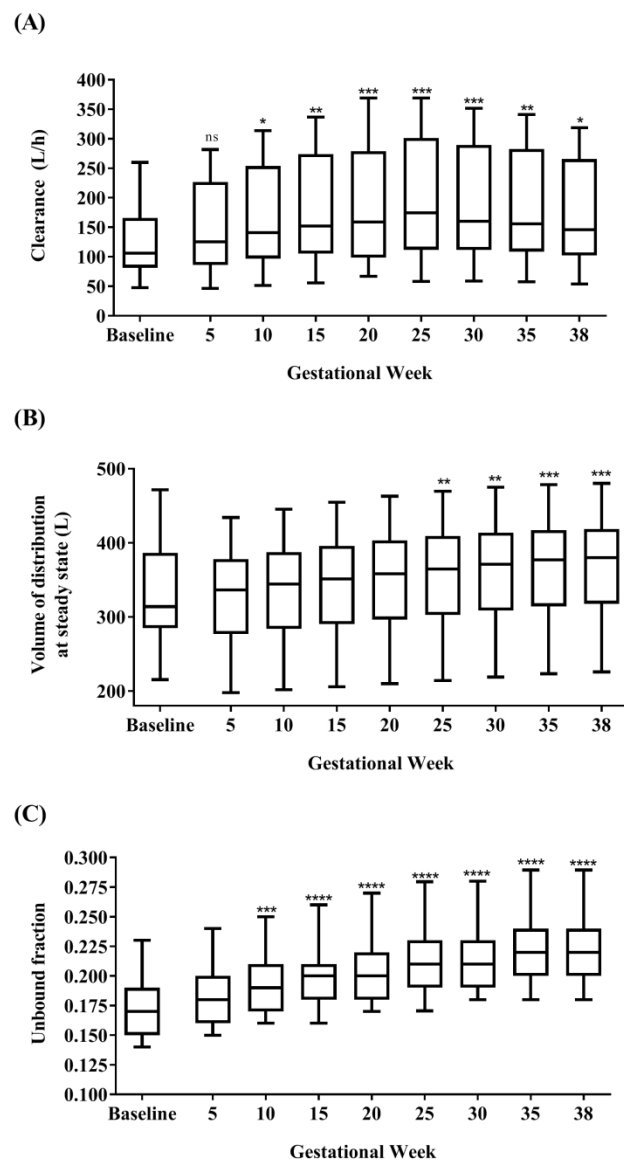


Figure 2

162x277mm (300 x 300 DPI)

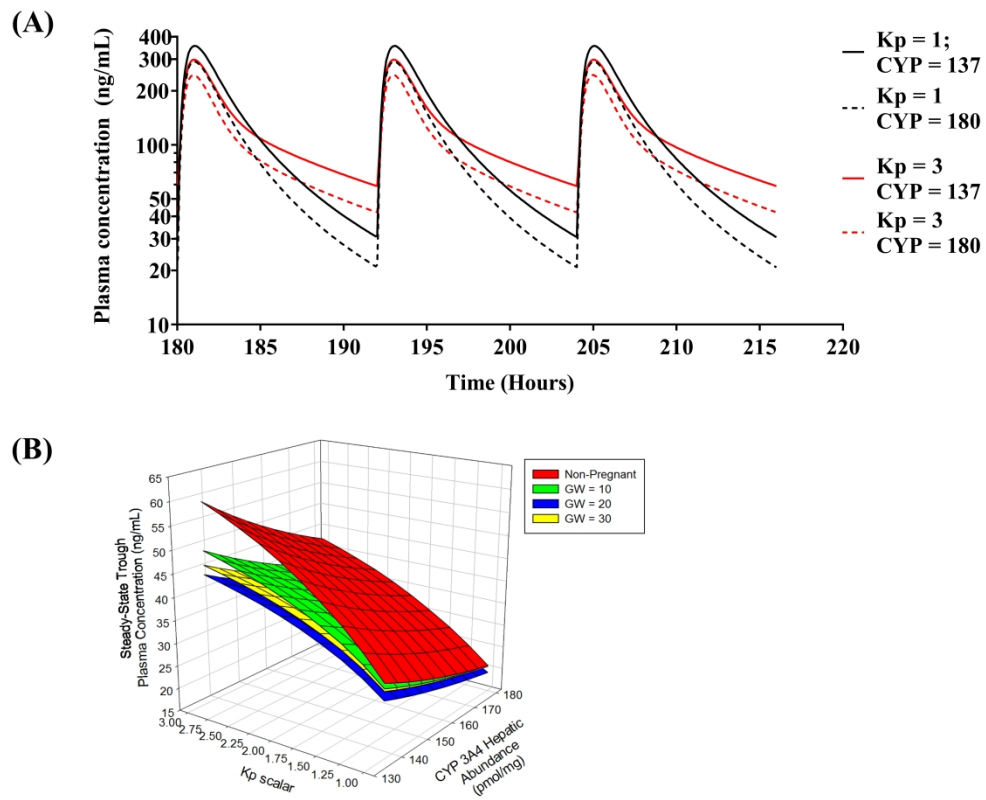


Figure 3

249x206mm (600 x 600 DPI)

