Published in final edited form as:

J Clin Psychopharmacol. 2018 February ; 38(1): 89–91. doi:10.1097/JCP.0000000000000820.

Quetiapine Dose Adjustments in Pregnant and Postpartum Women with Bipolar Disorder

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Atypical antipsychotics are increasingly used to treat Bipolar Disorder (BD) in women of childbearing age. In the United States, the rate of atypical antipsychotic use in pregnancy more than doubled between 2001 and 2007 [1]. A study of medication treatment in the United States from 2006–2011 identified quetiapine as the most commonly used second-generation antipsychotic in pregnancy [2]. In Denmark the rate of quetiapine use increased 83% among childbearing-aged women between 2009 and 2013, and in Australia quetiapine use tripled among pregnant women between 2000 and 2011 [3, 4]. Although BD and Schizophrenia are the FDA indications for treatment with quetiapine, off-label use of quetiapine has broadened, and it is increasingly prescribed for other diagnoses including insomnia, unipolar depression, and generalized anxiety disorder [5]. The few clinical practice guidelines for atypical antipsychotic use in pregnancy address the risk of fetal malformation, but pharmacokinetic and pharmacodynamic data for atypical antipsychotics, such as quetiapine, to inform dosing for optimal treatment throughout pregnancy are lacking [6].

The physiological changes of pregnancy that alter drug disposition include increased plasma volume, cardiac output, and glomerular filtration rate [7]. Steroid hormones (e.g., estradiol) also affect drug-metabolizing enzyme activities [8]. The concentrations of many psychotropic agents including selective serotonin-reuptake inhibitors (e.g., sertraline [9], citalopram [10], fluoxetine [11]), tricyclic antidepressants (e.g., nortriptyline [12]) and mood stabilizers (e.g., lamotrigine [13], lithium [14]), decrease across pregnancy. Dose changes are often necessary, as reduced plasma concentration-to-dose ratios of antidepressants and mood stabilizers in pregnancy are associated with increases in mood symptoms. This is particularly true for depressive symptoms for pregnant patients with bipolar disorder [10]. In a case report of quetiapine plasma concentrations across pregnancy, the changes in the area under the concentration versus time curve (AUC) in the first, second, and third trimester relative to six months postpartum were –27%, –42%, and –18% respectively [15]. These

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Conflicts of Interest: The Department of Psychiatry at Northwestern University received contractual fees for Dr. Wisner's consultation to Quinn Emanuel Urquhart & Sullivan, LLP (New York City), who represent Pfizer Pharmaceutical Company, in 2015. The remaining authors have no conflicts to report.

data indicate that plasma concentrations of quetiapine are lower in pregnancy compared to postpartum and that doses may need to be increased in pregnancy to maintain consistent plasma concentrations and efficacy. To add to the one report in the literature, we present data on ten cases of quetiapine dosing across pregnancy in women with DSM-IV diagnosed BD.

CASES

Women with BD (n=183) were enrolled in an observational trial at the University of Pittsburgh (Antimanic Drug Use in Pregnancy, R01 MH 075921, K. Wisner, PI) to characterize BD in pregnancy and evaluate the potential impact of pharmacotherapy on symptom course. The diagnosis of BD was confirmed by the Structured Clinical Interview for DSM-IV Axis I disorders. Among the women enrolled in the study, 29 took quetiapine at some point in pregnancy. Women were excluded if they took quetiapine inconsistently (n=4), were lost to follow-up (n=2), or only took quetiapine during the first trimester or late in the third trimester of pregnancy (n=13). Ten women who chose to continue taking quetiapine across pregnancy, reported compliance, and completed more than one study visit during pregnancy were included in our analysis. Women were between 19 and 40 years of age. Eight women were Caucasian, two were African American, and all were non-Hispanic. Diagnoses included BD I (n=6), BD II (n=2) and BD NOS (n=2). The choice to continue quetiapine pharmacotherapy was a decision each woman made with her community-based prescribing physician. Participants' prescribers managed quetiapine doses according to clinical assessment. This study was approved by the University of Pittsburgh IRB and all women provided written informed consent.

All subjects took immediate release quetiapine. The net dose changes across pregnancy and postpartum, along with concomitant medications, are presented in Table 1. Women completed an average of eight study visits that included mood assessments and self-reported medication changes since the last study visit. On average, women in this sample were followed from approximately 15 weeks gestation to six months postpartum. Eight of the ten women required dose increases during pregnancy, with an average increase of 175 mg. Reasons for dose increases included auditory and visual hallucinations (n=1), hypomanic episodes (n=2), and persistent depressive symptoms (n=5). One woman did not require a dose change during pregnancy and one required a dose decrease of 100 mg. The woman whose dose decreased across pregnancy was on a high preconception dose of quetiapine, which she discontinued due to pregnancy and then resumed at a lower dose at 16 weeks gestation. Dose changes were made variably across pregnancy and all women whose dose was titrated had at least one increase during the third trimester. Postpartum, only one of the eight participants for whom data were available continued taking quetiapine at the same dose used in pregnancy. Of the remaining participants, three discontinued quetiapine, three required a dose decrease, and one reduced quetiapine to as needed use. The seven women who took a lower dose or discontinued the medication postpartum cited sedation as the impetus for the change.

In addition to reporting medication use across time, patients were assessed for mood symptoms at set time points in pregnancy and postpartum. A trained clinician administered the Structured Interview Guide for the Hamilton Depression Rating Scale with Atypical

Depression Supplement (SIGH-ADS) [16] and the Mania Rating Scale (MRS) [17]. SIGH-ADS scores ranged from 3 to 44 during pregnancy and from 1 to 33 postpartum. Euthymic SIGH-ADS scores (defined as a SIGH-ADS score <9 [16]) constituted only 20% and 4% of assessments across pregnancy and postpartum, respectively. MRS scores were zero in 77.5% and 78.5% of assessments in pregnancy and postpartum, respectively. Scores on the SIGH-ADS and MRS were not correlated with quetiapine dose or dose changes; however, the protocol was not designed to capture mood assessments at the time of dose changes, which were not predictable.

All women had full term infants and no adverse birth outcomes were reported.

DISCUSSION

For the majority of women in this series, quetiapine dose increases were required during pregnancy, and after birth most women decreased or discontinued quetiapine due to side effects. All patients reported that dose increases or decreases were precipitated by symptom recurrence or side effects, respectively.

While the data from the women included in this report suggests that dose increases are needed in pregnancy and dose decreases are required postpartum for most women, it is important to note that one woman required no change and another woman required a dose decrease in pregnancy. The requirement for a dose change across pregnancy may be due to alterations in the function of hepatic cytochromes across childbearing. Quetiapine is predominantly metabolized by cytochrome P450 (CYP) 3A4, which is induced in pregnancy [18, 19]. Using dextromethorphan as a substrate, Tracey et al. reported a consistent increase in CYP3A activity across pregnancy [19]. The upregulation of CYP3A4 during pregnancy increases quetiapine elimination clearance and decreases quetiapine plasma concentration. Many of the women in this report were taking multiple medications, which were also metabolized by cytochrome P450 enzymes (e.g., CYP2D6) and impacted by the physiological changes of pregnancy. Additionally, some of the concomitant medications reported (e.g., nifedipine) can impact CYP3A4 and may have interacted with the metabolism of quetiapine. Interactions between quetiapine and concomitant medication during pregnancy and the impact on the course of treatment and BD illness need to be accounted for in future pharmacokinetic and pharmacodynamic studies.

Although the sample size is limited, our data suggest that pregnant women with BD should be monitored closely with monthly clinical evaluations across pregnancy to assess for worsening depressive symptoms and hypomanic or manic symptoms while taking quetiapine. Longitudinal quantitative clinician-administered or self-report assessments are useful tools to monitor patients for symptom worsening that signal a need to change the dose. If the dose is increased in pregnancy, it will need to be reduced postpartum to prevent side effects.

The data presented here add ten cases to the existing case report in the literature. More investigation on the pharmacokinetics and pharmacodynamics of quetiapine in pregnancy

and postpartum is needed to elucidate the timing and impact of metabolic changes on quetiapine concentration, effectiveness, and inter-individual variability.

Acknowledgments

Funding Source: National Institute of Mental Health (NIMH) R01 MH 075921, K.L. Wisner, PI. Dr. Clark was supported by PhRMA Foundation for the preparation of this article.

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Table 1

Quetiapine Dose Changes in Pregnancy and Postpartum

Subject ID	Pregnancy Dose Change (mg)	Postpartum Dose Change (mg)	Concomitant Medications ^a
1	↑ 50	No Data	PNV, Folic Acid
2	↑ 50	Discontinued	PNV, Nifedipine, Lamotrigine, Venlafaxine
3	↑ 150	Discontinued	PNV, Folic Acid, Antacid, Bupropion, Lamotrigine
4	↑ 450	↓ 350	PNV, B6, Iron, Heartburn Medication, Stool Softener, Prochlorperazine
5	↑ 50	↓ 25	PNV, Omega-3, Calcium, Fluoxetine
6	↑ 350	No Data	PNV, Heartburn medication, Iron, Sertraline
7	↑ 200	Initiated PRN dosing	Ibuprofen, Hydroxyzine, Aripiprazole
8	↓ 100	↓ 400	PNV, Docusate, Hydroxyzine, Antibiotics, Azithromycin, Oseltamivir, Topiramate, Lithium,
9	No change	No change	Acetaminophen, Bupropion
10	↑ 100	Discontinued	PNV, Omega-3

^aConcomitant medications include any medications that were taken concurrently with quetiapine at any point.

PNV=prenatal vitamins