

A Pilot Study of Prophylactic Management of Lamotrigine for Bipolar Disorder in Pregnant
Women

09-10-2018

Date: September 10, 2018

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Application Number: IRB000162134

JHM IRB - eForm A – Protocol

1. Abstract

The management of Bipolar Disorder during pregnancy is not simple. Studies have demonstrated that at least 80% of women who stop mood stabilizing medications for pregnancy relapse psychiatrically^{1,2}. However, relapse is also quite common in women who continue taking mood stabilizing medication with studies demonstrating approximately a 30-37% relapse rate-most with depressive episodes^{1,2}. Depression during pregnancy is associated with functional impairment and unhealthy behaviors in the mother, including higher body mass index, less prenatal care, higher rates of substance use, less healthy nutrition, and decreased rates of breastfeeding³⁻⁸. Untreated psychiatric illness in pregnancy is also directly correlated with worse neonatal and child outcomes, including significantly increased risks of preterm birth and low birth weight,³⁻⁸ increased cortisol levels in infants, and increased rates of child behavioral and emotional problems⁹⁻¹². Untreated antepartum depression is also one of the strongest risk factors for postpartum depression,¹³ which is associated with increased colic, impaired maternal-infant bonding¹⁴ and parenting behavior^{15 16}, worse child outcomes (including lower IQ, slower language development and behavioral disturbance¹⁷, and potentially devastating consequences including suicide and infanticide. Thus, many women with Bipolar Disorder choose to continue medication during pregnancy- but it remains unclear if there are specific approaches that will minimize their risk of relapse.

One likely explanation for the high relapse rate of Bipolar Disorder during pregnancy despite continued mood stabilizing medication is decreasing blood levels of mood stabilizing medications during the course of pregnancy. Pregnancy induces both pharmacokinetic and pharmacodynamic changes, which can result in decreased serum blood levels and decreased treatment efficacy. During pregnancy, the increased volume of distribution, alterations in hepatic clearance of drugs (including metabolism through cytochrome P450 enzymes), increased hepatic blood flow, increased glomerular filtration rate, and direct interactions with sex steroids¹⁸ can all lead to substantial differences in the drug dose-serum level relationship across pregnancy, with dramatic and rapid changes in the postpartum.

Therapeutic drug monitoring (TDM) is considered standard of care for a number of psychiatric medications – including those with a narrow therapeutic window, established therapeutic ranges, or significant variability in their pharmacokinetic properties. TDM can be an especially crucial guide to clinical treatment during pregnancy, but remarkably, there are no established protocols for the monitoring of levels and dosing of psychiatric medications in pregnancy. Most pregnant psychiatric patients are therefore managed based on symptom recurrence. In contrast, there are established protocols for monitoring blood levels and prophylactic management of antiepileptic medications for epilepsy, including lamotrigine which is also a mood stabilizing medication. We propose to collect pilot data on the psychiatric outcomes, adverse events, and obstetrical and infant outcomes of pregnant women with Bipolar Disorder who undergo prophylactic TDM for a commonly used mood stabilizing medication during pregnancy- lamotrigine. Our primary hypothesis is that prophylactic TDM for lamotrigine will result in a lower than expected rate of psychiatric relapse which, based on the literature, is approximately 30%. Along with testing this hypothesis we will collect adverse event data and obstetrical and infant outcomes to assess the safety of our protocol.

2. Objectives:

- a) **Specific Aim 1: Collect preliminary data on the psychiatric outcomes of pregnant women with Bipolar Disorder who undergo a TDM protocol for lamotrigine.** Hypothesis: Women undergoing a TDM protocol for lamotrigine will have a low rate (defined as <30%) of psychiatric relapse. Psychiatric outcomes will be defined by clinician interview, the Edinburgh Postnatal Rating Scale (EPDS) and the Young Mania Rating Scale (YMRS).
- b) **Specific Aim 2: Collect adverse event data from pregnant women with Bipolar Disorder undergoing a TDM protocol for lamotrigine.** Adverse event data will be collected using the UKU side effect semi-structured interview and the Frequency, Intensity, and Burden of Side Effects Rating (FIBSER) scale.
- c) **Specific Aim 3: Collect preliminary data on the obstetrical outcomes of pregnant women with Bipolar Disorder who undergo a TDM protocol for lamotrigine.** Obstetrical outcomes will be defined by review of the delivery admission chart by an obstetrician using the Peripartum Events Scale (PES).
- d) **Specific Aim 4: Collect preliminary data on infant outcomes whose mothers underwent a TDM protocol for lamotrigine.** Pediatric outcomes will be defined by review of the infant delivery chart by a pediatrician and by a neurobehavioral assessment using the Neonatal Intensive Care Unit (NICU) Network Behavioral Scale (NNS).

3. Background:

Evidence indicates that serum levels of lamotrigine decrease by 200-250% across pregnancy¹⁹, and that the clearance of lamotrigine can be increased 10-fold across pregnancy in many but not all women²⁰. In the epilepsy literature, levels between 2.5 and 15 have been reported for therapeutic efficacy with higher levels correlated with increasing signs of toxicity²¹. In the epilepsy literature, there is a published protocol for lamotrigine management before, during, and after pregnancy²² for seizure control as follows:

- *Prior to pregnancy, adjust lamotrigine dose to minimum effective dose to attain clinical stability. Obtain a reference concentration (RC), preferably when the patient is not taking oral contraceptives.*
- *During pregnancy, monitor lamotrigine concentration every 4 weeks. If serum concentration falls below RC, increase lamotrigine dose by 20-25% and re-measure serum level after 4 additional weeks. If serum level does not fall below RC, maintain same dose but check level again in four weeks.*
- *After pregnancy, obtain serum level within 1-2 weeks. IF level is above the RC, decrease dose by 20-25% and re-measure serum level in 1-2 weeks. Continue until RC is reached, and level is stable on two repeated checks. If patient had dose increased more than 3 times during pregnancy, do no wait until after delivery to obtain serum level; rather, implement first dose decrease (by 20-25%) in the first days following delivery, then monitor every 1-2 weeks as described above.*

In Bipolar Disorder, there has been one study examining lamotrigine blood levels in pregnant patients. Clark et al followed 8 women taking lamotrigine during pregnancy and obtained blood samples at 20, 30 and 36 weeks of pregnancy²³. They found that lamotrigine level to dose ratios were lower in pregnancy and increased in the postpartum time period with up to a 600% increase in the level-dose relationship after childbirth. The authors recommended that, based on their findings, psychiatrists should monitor lamotrigine levels on a monthly basis in pregnant women with Bipolar Disorder and prophylactically increase lamotrigine based on a pre-pregnancy or early pregnancy RC. They also recommended tapering lamotrigine (if increased during pregnancy) in the immediate postpartum time period. This recommendation has not been further tested for safety and it remains unclear if prophylactic TDM will prevent destabilization of Bipolar Disorder.

a)

4. Study Procedures

a. Study design, including the sequence and timing of study procedures

Our primary hypothesis is that prophylactic TDM for lamotrigine will result in a lower than expected rate of psychiatric relapse. The study will be an unblinded pilot study testing a TDM protocol for lamotrigine and will examine psychiatric, adverse event, obstetrical and infant outcomes. Because this is a pilot study we have chosen not to recruit a comparison group of women and instead focus on collecting outcomes for a larger sample of women who will undergo TDM for lamotrigine. Based on the literature we would expect the relapse rate in women who are maintained on their pre-pregnancy lamotrigine dosage to be at least 30%^{1,2}. Although our study design will not demonstrate superiority, it will provide preliminary evidence of efficacy and safety data for both the participant and her infant and will be the largest study examining a specific approach to managing lamotrigine during pregnancy in patients with Bipolar Disorder. We hope these data will then serve as a basis for a multisite randomized trial of prophylactic TDM for lamotrigine compared to treatment as usual in the future.

Pregnant women with Bipolar Disorder who are taking lamotrigine will be evaluated monthly during pregnancy including a clinical evaluation and a blood draw for lamotrigine levels at each visit. Based on the TDM protocol described below their lamotrigine dosing will be adjusted as needed based on their blood levels compared to the RC that was obtained prior to pregnancy or early in pregnancy while clinically stable. After delivery women and their infants will be assessed at 1, 2, 4, and 6 weeks postpartum.

Sample Size. We will recruit and follow up to 20 women with Bipolar Disorder who have chosen to take lamotrigine during pregnancy with a goal of maintaining a sample size of 16 allowing 4 drop-outs.

Recruitment. Participants will primarily be recruited through the Johns Hopkins Women's Mood Disorders Center (WMDC) and through referrals from the Obstetrics department. We will advertise on the WMDC Facebook site, the WMDC research site, EPIC and in local publications.

Lamotrigine Dosing Adjustments. At the time of study enrollment each participant will have a RC defined based on either 1) a pre-pregnancy serum level (for the current lamotrigine dosage) or 2) a serum level drawn at the time of enrollment. While we will preferentially use a pre-pregnancy RC since pregnancy hormone levels can affect lamotrigine levels, many psychiatrists do not routinely check lamotrigine levels and from a practical perspective we will obtain a lamotrigine at study entry to promote study participation and recruitment. Participants will be clinically well at the time of enrollment so that the serum level will be correlated with clinical stability. Lamotrigine levels will then be drawn monthly and the dose adjusted to maintain the RC. Specifically, if the monthly serum level is more than 0.5µg/mL lower than the RC, the dose will be adjusted by 20-25% and checked again at the next monthly visit. Higher levels than the RC are unlikely, since levels generally decrease across the course of pregnancy, but the dose will not be adjusted down unless there is a clinical indication (i.e. toxicity). Postpartum, all participants will be instructed to taper to the lamotrigine dose that was being taken at the time of the RC over the course of two weeks. While this does not follow the exact neurology, protocol described above (Background), we believe this approach makes sense since it will be more consistent and avoid the potential problem of toxicity. It also follows the recommendations of Clark et al²³.

Data Collection

a) **Maternal Psychiatric Outcomes:** We will monitor maternal psychiatric outcomes based on the EPDS, YMRS and clinical interview. The primary endpoint is the proportion of women who experience psychiatric relapse from the time of enrollment to 6 weeks postpartum. **Relapse** will be defined as one of the following: meeting SCID criteria for a Major Depressive Episode, meeting SCID criteria for a hypomanic or manic episode, development of high risk suicidal plan or attempt, or psychiatric hospitalization.

b) **Maternal Adverse Event Outcomes:** Adverse events will be monitored by using a semi-structured interview, (the UKU side effects rating scale) at every visit as well as the self-rated Frequency, Intensity and Burden of Side Effects Rating scale (FIBSER). Adverse events will be considered as related to the TDM protocol if they were not present at baseline or worsened in severity and were noted after a change in dosing. A preliminary analysis will be conducted comparing adverse events in participants who underwent dose increases during pregnancy to those that did not (assuming there are participants who did not undergo dosage increase).

c) **Maternal Obstetrical Outcomes:** Maternal obstetrical outcomes will be extracted from the delivery admission chart which will be reviewed by the study obstetrician, Dr. Hueppchen. The Perinatal Events Scale (PES) will be used to collect a majority of these outcomes including Past Obstetrics History, Medical Risk Factors, Obstetric Risk Factors, Progress in Labor, Method of Delivery and Complications. A preliminary analysis will be conducted comparing obstetrical outcomes in participants who underwent dose increases in pregnancy to those that did not (assuming there are participants who did not undergo dosage increase).

d) **Newborn Outcomes:** Newborn outcomes will be extracted from the delivery admission chart which will be reviewed by the study pediatrician, Dr. Katznelson. We will use the infant outcomes portion of the Peripartum Events Scale (which includes Apgar scores and Infant Complications) and, in addition, collect infant weight, measurements, gestational age and need for medical interventions or NICU admission. A preliminary analysis will be conducted comparing infant outcomes for participants who underwent dose increases during pregnancy to those that did not (assuming there are participants who did not undergo dosage increase). All infants will also undergo a neurobehavioral assessment at weeks 2, 4 and 6 postpartum using the Neonatal Intensive Care Unit (NICU) Network Behavioral Scale (NNS). Our research assistant will receive training at the Brown Center for the Study of Children at Risk which has a standardized training on the use of NNS. The NNS will be used to identify any infant neurobehavioral effects of the TDM protocol. A preliminary analysis will be conducted comparing infant neurobehavioral outcomes for participants who underwent dose increases during pregnancy to those that did not (assuming there are participants who did not undergo dosage increase).

- b. **Study duration and number of study visits required of research participants.** Each subject will be seen approximately 12 times across the course of the study. We will attempt to recruit subjects who are less than 20 weeks pregnant and will plan for monthly study visits during pregnancy. Women and their infants will also be assessed after delivery at 1, 2, 4, and 6 weeks postpartum. We expect that most study visits will take place in the Women's Mood Disorders Center, however home visits by research assistants will be used if a participant cannot come to the Center (for example if a participant is on bedrest) to maintain participation and continuity.
- c. **Blinding, including justification for blinding or not blinding the trial, if applicable.** Not applicable. Subjects will be receiving the drug that is part of their usual care and we will be collecting pilot data.
- d. **Justification of why participants will not receive routine care or will have current therapy stopped.** Participants will undergo more clinical care than is currently routine in that they will be monitored on a monthly basis and their lamotrigine dosing adjusted as part of a TDM protocol.
- e. **Justification for inclusion of a placebo or non-treatment group.** There will be no placebo or non-treatment group.

- f. **Definition of treatment failure or participant removal criteria.** Participants will be removed from the study if they meet criteria for Relapse as described above. Participants will also be removed if they are lost to follow-up or are noncompliant with the study protocol.
- g. **Description of what happens to participants receiving therapy when study ends or if a participant's participation in the study ends prematurely.** Participants will return for clinical care to their outpatient provider at the end of the study or if their participation ends prematurely.

5. Inclusion/Exclusion Criteria

Inclusion Criteria. Pregnant women with a history of Bipolar Disorder (Bipolar Disorder I, Bipolar Disorder II or Bipolar Disorder not otherwise specified) who are taking lamotrigine and who intend to continue lamotrigine through pregnancy will be enrolled. All participants must be in the first 20 weeks of pregnancy at the time of enrollment. All participants must also be on stable doses of lamotrigine (for the past 4 weeks), have an EPDS <13, a YMRS <12 and be judged by the study clinician to be clinically stable. Participants may be taking other psychiatric and nonpsychiatric medications.

Exclusion Criteria. Participants who have active suicidal ideation or who are clinically unstable will be excluded. Participants who are dependent on alcohol, marijuana or other substances in the 90 days prior to study entry will be excluded.

6. Drugs/ Substances/ Devices

- a. **The rationale for choosing the drug and dose or for choosing the device to be used.** Lamotrigine is an evidence-based treatment for Bipolar Disorder in pregnancy. The rationale for our TDM/dosing regimen is based on recommendations in the epilepsy literature. There is currently no established protocol for the dosing of these drugs in pregnant patients with Bipolar Disorder.
- b. **Justification and safety information if FDA approved drugs will be administered for non-FDA approved indications or if doses or routes of administration or participant populations are changed.** There are no drugs with FDA approval for the management of mood disorders in pregnancy. Therefore, we must use FDA approved drugs for non-FDA approved indications, a common clinical practice.
- c. **Justification and safety information if non-FDA approved drugs without an IND will be administered.** Not applicable.

7. Study Statistics.

We will perform descriptive statistics that include percent tabulations for categorical variables, means with standard deviations for continuous variables, and medians with ranges where more appropriate. The primary endpoint is the proportion of women who experience psychiatric relapse from the time of enrollment to 6 weeks postpartum. Relapse will be defined as one of the following: meeting SCID criteria for a Major Depressive Episode, meeting SCID criteria for a hypomanic or manic episode, development of high risk suicidal plan or attempt, or psychiatric hospitalization. We do not have a comparison group but would normally expect a relapse rate of approximately 30% based on the literature We will also collect and describe adverse events, obstetrical and infant outcomes.

8. Risks.

a) **Medical Risks.** The risks and discomforts are expected to be minimal and rare. During interviews, the participants may experience some discomfort or anxiety because of the personal nature of the questions. There may be some risk that the research participant may find the diagnostic interview uncomfortable or feel it is an invasion of privacy. Venipuncture may be associated with the momentary discomfort of the needle stick, fainting, bruising and rarely infection. There is also a risk for loss of confidentiality. Other risks include maternal side effects or toxicity from lamotrigine, infant side effects or toxicity from lamotrigine, and maternal psychiatric relapse.

b) **Steps Taken to Minimize Risks:**

Interviews, Questionnaires: A trained research assistant will be available at all times while the participant is filling out questionnaires. The Principal Investigator will also be available by telephone, and WMDC clinicians (including a psychiatrist) will be onsite during the administration as well. Should the participant become distressed, the study staff member can provide reassurance and evaluate her psychiatric state. Participants will be informed during screening and consenting procedures that they do not have to answer or complete tasks that cause them distress. Each participant will be directed to inform the study team member if she wishes to skip a certain part. If the study staff member determines that the participant is experiencing a psychiatric emergency, the steps listed below under that heading will be taken.

Blood draw: In order to decrease the risks associated with venipuncture, we will employ staff that is experienced in blood drawing procedures.

Psychiatric Urgency/Emergency: Management of Psychiatric Urgency/Emergency: In order to minimize the risk of suicide, we will follow the following procedures for protection against this risk:

- Each participant will be asked directly at every visit whether or not they are having thoughts about harming themselves or anyone else, including their child/children. All study personnel have (or will have) experience in interviewing participants with psychiatric disorders and will have been trained how to handle reports of suicidal ideation or threats of harm to others – including when to call 911 or campus security.
- The study psychiatrists will be available by pager to the participants and the research assistants during the study.
- An emergency contact information sheet will be maintained at each clinical site on each participant including telephone contacts, an emergency contact person, the participant's psychiatric outpatient treatment provider's name and contact information and the participant's home address as well as contact information for the participant's obstetrician and the infant's pediatrician. This will provide important information in case of psychiatric or medical urgency/emergency. All participants will sign a release of information form in order to allow study personnel to contact their emergency contact and/or providers if necessary during the study.
- If a participant who reports suicidal or otherwise harmful thoughts (to themselves or others) is judged to be at risk by the study psychiatrist, they will be taken to the Emergency Room/Emergency Mental Health. The Emergency Room is on the same campus as the study sites. If the participant is interviewed by phone and is judged to be at risk, the participant will be instructed to go to the emergency room and if there is a question regarding

compliance with this request the study psychiatrist will call 911 as well as the emergency contact information maintained for each participant. If the participant is interviewed by phone and is judged to be at imminent risk of suicide, the study psychiatrist will call 911 and have the police complete a welfare check.

- If the participant is not at risk of harming herself or others but is psychiatrically ill, the study psychiatrist will provide clinical care as necessary until the participant can be seen by her treating outpatient clinical psychiatrist. The participant will remain in the study and undergo all study visits and procedures as long as consent continues.

Obstetrical Urgency/Emergency: Should one of the participants develop an urgent obstetrical problem, the participant will either be taken to the local Obstetrics and Gynecology Clinic or Emergency Room, whichever seems more appropriate. Both the Clinic and the Emergency Room are on the same campus as the study site. The subject's private obstetrician will also be contacted.

Lamotrigine toxicity: Every participant will be monitored closely for side effects/signs of toxicity during the trial. Because the RC will be established prior to pregnancy or early in pregnancy we anticipate that the likelihood of significant side effects or toxicity in the participants is very low. If a participant does develop side effects or signs of toxicity the dose of lamotrigine will be lowered by the study psychiatrist. At every visit the participant will fill out a Frequency, Intensity and Burden of Side Effect Scale (FIBSER) to monitor for significant side effects from the protocol. Obstetrical outcomes will be assessed by Dr. Hueppchen from the Gynecology and Obstetrics Department.

Neonatal toxicity: It is possible that increased dosing of lamotrigine during pregnancy will lead to increased side effects or toxicity in the newborn. We do not anticipate this outcome since the protocol is used in the management of seizure disorders and there have not been reports of adverse effects in infants whose mothers participate in these protocols. We will monitor for this potential risk by collecting neonatal outcomes via a review of the medical record by a pediatrician (Dr. Katznelson) and by undergoing a neurobehavioral exam using the Neonatal Intensive Care Unit (NICU) Network Behavioral Scale (NNNS) at 2, 4, and 6 weeks postpartum. Our research assistant will undergo specialized training at Brown University in order to conduct the exam appropriately.

Neonatal Intensive Care Unit (NICU) Network Behavioral Scale (NNNS) Examination: The NNNS is a standardized neurobehavioral exam that is used in infants. It primarily consists of observation of the infant, reflex testing and holding the infant. The primary risk is that the infant will become upset and cry. Our research assistant will have undergone an intensive 5 day training at Brown and will learn as part of the training how to minimize this risk.

c) Plan for reporting unanticipated problems or study deviations.

Reports will be made to the IRB and necessary healthcare providers in the event of an unanticipated problems or study deviations. The study team will follow IRB protocol to determine if a deviation or problem needs to be reported immediately or if it can be reported at the yearly continuing review. All serious adverse events will be reported to the IRB immediately by the PI.

d) Legal Risks:

Confidentiality: Careful procedures will be employed to protect the confidentiality of all participants. Participants will be assigned unique ID identifiers not associated with personally

identifying information. These will be used on all interview protocols and lab results. No identifying information other than the unique ID will appear on interview protocols. All data files and analyses will be performed on research computers using only code numbers to identify participants. Only summaries of group data will be reported in any publications or presentations, with no identification of individuals. All study personnel will maintain their certification in the Protection of Human Subjects training program prior to participating in the research. Only authorized persons will be granted access to enter and view study data. Subject IDs with subject names will be kept in CRMS and only designated personnel on the research team will have access. Charts containing subject data for active subjects will be kept in a locked filing cabinet or room and will be identified only by subject ID. All precautions will be taken to protect the confidentiality of the study participants. As with participation in any research study there is a slight risk of a breach in the security procedures that would affect the confidentiality of the research participant. Every effort will be employed to minimize this risk. If such a breach occurs, the research participant will be informed as well as the IRB.

Additional Protections for Pregnant Women, Human Fetuses and Neonates. This study meets all requirements for research in this vulnerable population as described by DHHS regulations and OHRP guidance. This study is essentially an observational study with blood and clinical data collection only and no active study intervention that increases the risk beyond what the woman and her child would face outside of participation in the study.

9. Benefits

Participants will be paid for their time and will undergo more regular psychiatric evaluation than is standard for most psychiatric patients. Participants may avoid psychiatric relapse by participating in the study due to the increased monitoring of lamotrigine blood levels and adjustment of lamotrigine dosing.

Developing more effective management strategies for bipolar disorder during pregnancy will allow us to decrease the associated maternal and infant morbidity and mortality by working towards decreasing the relapse rate during the perinatal time-period.

10. **Payment and Remuneration. Detail compensation for participants including possible total compensation, proposed bonus, and any proposed reductions or penalties for not completing the protocol.** Participants will be compensated for parking or taxi service for their visits. In addition, they will receive compensation up to the amount of \$450 if they complete the entire study. If the participant fails to complete all visits, they will be paid based on the visits spent in the study: Participants will be paid \$25 for each pregnancy visit completed and \$75 for each postpartum visit. If participants opt for a home visit postpartum, they will receive \$50 instead. Participants will also be paid a bonus of \$100 for achieving a minimum of 5 pregnancy visits and 2 postpartum visits in order to encourage continuity of participation. Lab costs for lamotrigine levels will be covered by the study as well. If acute medical care or medical or psychiatric hospitalization is required during the course of the study, the individual participant and/or their health insurance will be expected to cover those costs.

11. Costs

The participant and her insurance company will cover the cost of lamotrigine and any other prescribed medications. The study will cover the cost of the lamotrigine blood draws and laboratory processing. If acute medical care or medical or psychiatric hospitalization is required during the course of the study, the individual participant and/or their health insurance will be expected to cover those costs.

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