

Medication management of bipolar disorder during the reproductive years

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Abstract

The management of bipolar disorder during reproductive years is a challenge to both patient and clinician. The rapidly changing landscape of medical literature, newly available medications, and implementation of the Pregnancy and Lactation Labeling Final Rule by the Food and Drug Administration can be dizzying. This article serves as a brief, practical guide on the use of medications for the treatment of bipolar disorder before, during, and immediately after pregnancy. Special focus is devoted to the risk-benefit analysis of using potentially teratogenic medications during pregnancy. Availability and appropriateness of various contraceptive methods and folic acid supplementation in combination with mood stabilizers is also addressed. Every clinician managing bipolar disorder in adult women should be knowledgeable of family planning resources and what to do in the setting of unintended pregnancy.

Keywords: pregnancy, bipolar disorder, mood stabilizer

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Introduction

Over the past 10 years, great strides have occurred in research, reporting, and labeling regulations of psychiatric medication use during pregnancy. There is now a wealth of evidence to make informed medication choices that balance risks and benefits to both mother and baby in the treatment of bipolar disorder. However, although there is an abundance of studies in women of childbearing potential, this body of information is still plagued with epidemiological pitfalls of pregnancy studies. For exam-

ple, because of ethical concerns, randomized controlled trials are not feasible during pregnancy. Also, in order to detect significant differences of extremely rare occurrences, study groups would need to enroll thousands of subjects, which is cost- and time-prohibitive.¹

In 2009, the American Congress of Obstetricians and Gynecologists and the American Psychiatric Association released a joint report² on the management of depression during pregnancy. This guideline filled a gaping hole in medical literature to direct practitioners and patients toward safe, effective antidepressant use. Although these guidelines serve as direction on the use of antidepressants in the perinatal phase, there is no official stance on the use of antipsychotics or mood stabilizers during pregnancy. Despite emerging studies examining medication safety during pregnancy and support from the Food and Drug Administration (FDA) for drug manufacturers to study this population, the medical literature is rife with epidemiological pitfalls limiting the quality of research. The scope of this article is to provide a brief and comprehensive review of medication risks in bipolar disease during each trimester of pregnancy. Often, the lay media will report on individual studies that can invoke fear and uncertainty in both patients and clinicians. This article comprises a broad survey of

currently available literature as, when one examines a single study in isolation, one can glean a narrower interpretation compared to examining an entire body of literature.

A comprehensive discussion on this topic is especially timely given the recent FDA labeling changes. The FDA has replaced pregnancy categories, which have been in effect since 1979, with narrative sections to reflect a true risk-benefit analysis.³ The narrative sections allow for the clinician to examine data available rather than the previous ranking system, which was unclear and incomplete. For example, clozapine and lurasidone were both previously designated Category B, implying they are safer in pregnancy than Category D, but they have the least amount of data of all antipsychotics available in human pregnancy. Conversely, benzodiazepines are Category D; however, this drug class is a mainstay of treatment in the management of acute mania, severe anxiety, and postpartum psychosis.^{4,5} The Category D status of benzodiazepines should never serve as an absolute contraindication to use in pregnancy in the setting of these life-threatening scenarios.

Case #1

A 24-year-old female with bipolar disorder, who is 12 weeks pregnant, is admitted to the psychiatric hospital. The psychiatric team is uncomfortable managing both bipolar disorder and pregnancy. An ob-gyn consultation is obtained, resulting in a recommendation to initiate lurasidone as the resident heard it was Category B. What education points would you make to the obstetrics team regarding pregnancy and lactation labeling?

Discussion

Although lurasidone was previously designated Pregnancy Category B, these categories are now obsolete. Lurasidone's prescribing information now contains a narrative section describing human and animal risk in accordance with the FDA's Pregnancy and Lactation Labeling Final Rule. This new narrative format allows clinicians to read the available current data and make an informed decision rather than relying on a predetermined "grade" that was often outdated, inaccurate, or based on lack of evidence.

Because a woman spends 50% of her life span in reproductive years and risky behaviors and hypersexuality are symptoms of mania, the likelihood of treating bipolar disorder during pregnancy is high. Additionally, pregnancy and the postpartum period are phases of excessive stress and vulnerability, making psychiatric relapse often inevitable for women with bipolar disorder. Discontinuation of mood stabilizers during pregnancy further increases the risk of relapse as 85% of women who stopped their mood stabilizer relapsed compared to 37% of women who continued taking their mood stabilizer.⁶ In addition to the increased

Take Home Points:

1. In the prepregnancy phase, all women with bipolar disorder should be counseled on adequate folic acid supplementation, risk of divalproex and pregnancy, reliable contraception (eg, utility of long-acting reversible contraception) and potential drug-drug interactions with some mood stabilizers and hormonal contraception.
2. Drug exposure during the first trimester is more precarious than other trimesters. This is a period of organogenesis, exposing a fetus to possible major congenital malformations. The baseline risk of major congenital malformations is 1% to 3% in the general population without any drug exposure.
3. The period of time immediately after delivery is unpredictable for a mother's mental health due to the risk of postpartum psychosis, massive fluid and hormonal shifts, and the pressures of caring for a newborn. Heightened psychiatric monitoring should occur during this period in order to identify relapse early.

risk of affective relapse, untreated bipolar disorder during pregnancy has been associated with adverse pregnancy outcomes, such as a small-for-gestational-age infant, microcephaly, and neonatal hypoglycemia.⁷

Before Pregnancy

Any woman of reproductive age with a bipolar disorder diagnosis and taking a mood stabilizer should be mindful of the following: (1) adequate folic acid supplementation, (2) drug-drug interactions with antiepileptics and oral contraception, and (3) the utility of long-acting reversible contraception (LARCS) in preventing an unplanned pregnancy. Prepregnancy family planning services, from counseling to referrals to women's health providers, should be offered often to women of childbearing potential in the psychiatric setting to ensure a comprehensive approach to treatment. At a minimum, clinicians should provide reassurance of the low rate of teratogenicity of psychiatric medications should an unintended pregnancy occur.

For a woman taking an antiepileptic associated with neural tube defects, such as carbamazepine or divalproex, it is recommended she take folic acid 4 mg daily (in contrast to the 1 mg daily recommended to women not on an antiepileptic).⁸ Clinicians should be aware there are no over-the-counter (OTC) supplements that contain enough folic acid for high dose supplementation. A standard adult OTC multivitamin contains folic acid 400 mcg, and an OTC prenatal vitamin contains folic acid 800 mcg. Folic acid 1 mg tablets are available via prescription only; the

implication of this availability is OTC use would require a woman to take 10 tablets, an unreasonable pill burden.

Divalproex is a known teratogen, associated with both neural tube defects and irreversible cognitive impairment as demonstrated by lower IQ scores in children exposed in utero, especially in doses greater than 1000 mg/day.^{9,10} For this reason, divalproex should not be considered as a first-line agent for the purpose of mood stabilization in women of childbearing potential. If it is used in this population, a LARC such as an intrauterine device or progestin implant is recommended.

Carbamazepine, a known pan-inducer of the cytochrome P450 enzyme system, is associated with reduced oral contraceptive efficacy.¹¹ For that reason, a copper intrauterine device may be used to prevent unwanted pregnancy.

Lamotrigine, an antiepileptic FDA approved for maintenance treatment of bipolar disorder, is associated with lower efficacy during times of estrogen supplementation in an oral contraceptive cycle due to increased clearance. Similar to valproic acid, a progesterone-only containing product or a LARC would be useful at preventing pregnancy while maintaining mood stabilizer efficacy without having to monitor lamotrigine serum concentrations.^{12,13}

The increasing availability of a variety of birth control options over the past 15 years allows for a woman to make informed choices that are most suitable for her lifestyle and concomitant disease states. Generally, LARCs should be recommended for women with bipolar disorder due to low failure rates, ability to get pregnant immediately after removal, and ease of use.¹⁴

Unintended pregnancies occur at a rate of 40% to 50% and possibly at higher rates in patients with bipolar disorder.⁴ Many women and clinicians are fearful of medication exposure during pregnancy, and there is cause for concern with some medications. However, the risk of relapse due to medication discontinuation is real and should be considered when evaluating medication use during pregnancy. When evaluating any medication exposure during pregnancy, the first question to ask is “which trimester?” Risk to the fetus will depend largely on dose, duration, and the trimester of exposure.

Managing Bipolar Disorder During Pregnancy

First Trimester

The first trimester is the period of organogenesis; therefore, major congenital malformation risk is highest with drug exposure in this time period. When considering

the risk of major congenital malformations, it is imperative to remember the baseline risk of 1% to 3% in the general population.¹⁵ Clinicians should remember this statistic to assist in balancing risks versus benefits of drug exposure. Additionally, clinicians should avoid using sensational language employed by both the lay media and medical literature. For example, “double the risk” of a malformation (ie, describing in terms of relative risk compared to lack of exposure) sounds frightening. However, if the baseline risk is extremely low, perhaps the risk is acceptable when compared with the risk of untreated disease.

Divalproex is associated with an increased risk of neural tube defects, necessitating supra-therapeutic folic acid supplementation (4 mg/daily). The neural tube closure is complete at 28 days postconception; after this time, folic acid will not be effective at preventing neural tube defects. Other major congenital malformations associated with divalproex include cardiac defects, craniofacial defects, and hypospadias.¹⁶ Although there is an increased risk of these malformations, the absolute risk is nominal. Heart malformations were associated with an odds ratio (OR) of 1.6 to 3.3, and CNS malformations were associated with an OR of 2.5 to 12.7. Of particular significance is the OR of 12.7 for spina bifida in infants exposed to divalproex in the first trimester. This provides further support that divalproex should be reserved as a second- or third-line agent in the treatment of bipolar disorder during reproductive years.¹⁷

Lithium was long thought to be associated with a clinically significant increased risk of the Ebstein anomaly, in which an abnormal tricuspid valve is displaced downward into the right ventricle. Initial reports characterized the Ebstein anomaly as being 400 times more likely in an infant exposed to lithium during the first trimester.¹⁸ The Ebstein anomaly is described as having a baseline, general population risk of 1 in 20 000 live births. From 1973 until 1994, the assumed risk of lithium exposure during the first trimester was 1 in 400 live births. However, upon reexamination of the literature, it was demonstrated that the Ebstein anomaly post lithium exposure was exaggerated. True incidence is closer to 1 in every 1000 to 2000 births.^{19,20} When making this comparison with absolute risk terminology, although lithium is associated with an increased risk of cardiac malformations, the overall risk is still negligible. This characteristic has become such a notable feature about lithium it is included in many medical school examinations, perhaps leading to an implicit bias against lithium use in pregnancy.

Lamotrigine has had mixed studies implicating exposure with higher infant risk of cleft palate. Some studies show an increased risk of oral cleft defects, and others find no

association.²¹ This discrepancy is quite common in pregnancy literature as there are many epidemiological pitfalls, such as recall bias, small sample sizes, and an inability to control for maternal illness. Generally, lamotrigine during pregnancy can be cautiously used with pregnancy being 1 of the few reasons to monitor lamotrigine levels as serum concentrations may decrease as the pregnancy progresses. Although no target therapeutic range has been defined for mood stabilization or even epilepsy, therapeutic drug monitoring of lamotrigine is recommended in the pregnant patient. A prudent method of heightened monitoring would be to obtain a baseline, prepregnancy lamotrigine serum concentration and then obtain serum concentrations monthly thereafter. Lamotrigine levels will decrease as much as 50% as the pregnancy progresses, and lamotrigine doses will need to be increased accordingly to maintain efficacy.²²

Carbamazepine, already a complicated medication to use due to its pan-induction of metabolic enzymes, has been associated with an increased risk of spina bifida.²³ However, a recent retrospective analysis of 240 071 cases examined the risk of congenital malformations in fetuses exposed to lamotrigine, carbamazepine, or divalproex. The rate of congenital malformation in the carbamazepine (and lamotrigine) groups was comparable to the unexposed group.²⁴

Antipsychotics, often used for their mood-stabilizing properties in bipolar disorder, have not shown signals for major congenital malformations.²⁵ Because of the relative safety of antipsychotics during pregnancy and the decades of use in pregnancy, a first-generation antipsychotic may be preferable over a second-generation antipsychotic (SGA) despite previous pregnancy categories. First-generation antipsychotics have been used since their introduction to the market more than 5 decades ago for the management of hyperemesis gravidarum, particularly phenothiazines (chlorpromazine) and butyrophenones (haloperidol).^{26,27} However, when selecting an antipsychotic, it is important to consider adverse effects that affect quality of pregnancy. For example, restless legs and constipation are known irritants in pregnancy, so choosing an antipsychotic with a low anticholinergic burden and low propensity to cause akathisia is advisable. An SGA, such as risperidone, with a streamlined receptor affinity profile may be preferred.

Because of an abundance of case reports during the 1970s, benzodiazepines were once thought to be associated with an increased risk of oral cleft and other major congenital malformations. More recent, comprehensive literature does not show an increased risk of malformations with first-trimester benzodiazepine exposure.²⁸

Second Trimester

The second trimester of pregnancy is a time when many discomforts of the first trimester dissipate, such as morning sickness and fatigue. During this period, the fetus is developing skeletal structures and lungs. Fewer medication considerations are necessary during the second trimester with the exception of divalproex exposure and metabolic complications of SGAs.

Divalproex is not only a known teratogen during first-trimester exposure, but it also has been associated with toxicity to the central nervous system of the developing fetus. Children exposed to high-dose divalproex (greater than 1000 mg total daily dose) during pregnancy were found to have IQ scores 7 to 10 points lower than children exposed to carbamazepine, lamotrigine, and phenytoin.²⁹

If an SGA is utilized, metabolic monitoring should be done during the second and third trimester via blood pressure and glucose monitoring. The standard glucose tolerance test should be completed during the second trimester to assess for gestational diabetes. Although it would be biologically plausible to see an increased rate of gestational diabetes in women taking olanzapine, no signal has been observed beyond the occasional case report.³⁰

Clearly, abdominal circumference should not be a measurement of metabolic syndrome during pregnancy, and even lipids will be elevated during pregnancy. During a normal pregnancy, triglycerides, total cholesterol, HDL, and LDL are higher, making a fasting lipid panel as part of monitoring for metabolic syndrome irrelevant.³¹

Third Trimester

The third trimester is primarily a stage of growth and organ maturation rather than organ system development. Although teratogenicity is not a concern, drug exposure during the third trimester has been associated with a withdrawal or discontinuation syndrome in the infant shortly after birth. For example, in 2011, the FDA updated labeling on antipsychotics to include a warning for abnormal muscle movements and withdrawal symptoms in newborns. This warning was based on 69 cases of neonatal extrapyramidal symptoms reported to the Adverse Event Reporting System.³² Of note, this type of warning system based on maternal or clinician report is not epidemiologically sound due to a high amount of recall bias. Additionally, at birth, a well-defined process of neonatal adaptation occurs. Part of that neonatal adaptation to the extrauterine environment is a release of catecholamines, which may explain some perceived withdrawal symptoms, such as abnormal movements or jitteriness.^{33,34}

Benzodiazepine exposure during the third trimester has been implicated in a withdrawal or discontinuation syndrome in neonates, specifically defined archaically as “floppy baby syndrome.” Modern literature does not correlate a causal relationship between benzodiazepine use and neonatal discontinuation, but rather, signals seen are related to maternal illness or other factors.³⁵

An increased volume of distribution and glomerular filtration rate likely means a woman’s lithium dose will need to be increased based on serum concentrations. Up until the third trimester, obtaining monthly lithium serum concentrations is an appropriate monitoring parameter. During the last 3 months of pregnancy, it is recommended to assess lithium serum concentrations every 1 to 2 weeks with the expectation of lithium clearance doubling, thereby lowering serum concentrations and increasing relapse risk. Conversely, lithium therapy should be held at the onset of labor in order to avoid lithium toxicity immediately postpartum. Although there are no specific recommendations on how long to hold lithium, generally a time frame of 24 to 48 hours postdelivery will allow enough time for volume redistribution.³⁶

Case #2

A 28-year-old female who is 32 weeks pregnant with her first child presents to the emergency department with no sleep for 48 hours, flight of ideas, grandiosity, and hyper-religiosity. She explains in uninterruptable speech that when she found out she was pregnant, her obstetrician instructed her to stop taking lithium and risperidone, which she had been stable on for 3 years after her first manic episode and Bipolar 1 diagnosis.

Discussion

Unfortunately, many clinicians continue to harbor misinformation about psychotropic medication use during pregnancy and will recommend discontinuation. It is still common for pregnant women to present for hospitalization in the setting of a clinician-recommended discontinuation of mood stabilizers and antipsychotics. Because of the risk to the patient and her unborn child, implementing treatment for mania rapidly is imperative to maintain safety. Restarting lithium and risperidone would be appropriate given the patient’s previous response and stability on this combination.

“Fourth” Trimester

Although not a recognized medical term, the fourth trimester, or the first 3 months after delivery, can be a challenging time period for new mothers. A woman with bipolar disorder is more likely to experience affective

complications postdelivery as sleep deprivation worsens while caring for a newborn.³⁷ Questions that arise may include the following: How does a woman care for herself and her infant in the first 3 months of life? What are good resources for medications and lactation? Which medications will inhibit or promote lactation?

Postpartum psychosis is more likely to develop in a patient with bipolar disorder compared to the general population.³⁸ Typically, onset of symptoms will occur within the first week after delivery as a diagnosis of bipolar disorder is associated with an earlier onset of postpartum psychosis. Those without a bipolar diagnosis will typically develop symptoms in the first 2 to 3 weeks postdelivery. It is a true psychiatric emergency and should be treated accordingly as it has been implicated in infanticide and suicide. Fortunately, the treatment of postpartum psychosis is generally well defined: benzodiazepines, antipsychotics, and lithium are foundational pharmacotherapy.⁵

If lithium is reinitiated, it absolutely should not be restarted at the predelivery dose as a massive fluid shift has occurred and glomerular filtration rate returns to prepregnancy status. Restarting at the predelivery dose will result in lithium toxicity. Instead, it is recommended to restart the prepregnancy dose. One should not anticipate gastrointestinal distress associated with lithium reinitiation as lithium’s half-life is approximately 24 hours, and thus, it will not have completely cleared during the peridelivery period in which it was held.

Women in the immediate postpartum phase are encouraged to take scheduled nonsteroidal anti-inflammatory drugs to prevent cramping associated with uterine contraction. Because of the well-known interaction of lithium and nonsteroidal anti-inflammatory drugs, using an alternative medication, such as acetaminophen, would be prudent. If a woman is not breastfeeding, aspirin or sulindac may also be considered for postpartum pain in the setting of lithium use.

Conclusion

Managing pregnancy and bipolar disorder can be cumbersome and frightening to the clinician and patient. However, emerging data continue to demonstrate the necessity of continuing treatment during pregnancy and the relative safety of psychiatric medications. Applying a few attentive parameters to decide risk to the fetus and mother can assist clinicians and patients in having thoughtful discussions about continuing pharmacotherapy throughout the gestational period. These parameters include (1) identifying trimester of exposure and associated risks, (2) therapeutic drug monitoring and dosage adjustments as the pregnancy progresses, and (3)

weighing untreated maternal illness risks against fetal harm risk.

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