CNS SPECTRUMS

CME Review Article

Between a Rock-a-bye and a Hard Place: Mood Disorders During the Peripartum Period

This activity is provided by the Neuroscience Education Institute.

Additionally provided by the American Society for the Advancement of Pharmacotherapy.

American Society for the Advancement of Pharmacotherapy
Division 55, American Psychological Association

CME Information

Date of Release/Expiration

Released: December, 2017
CME credit expires: November, 2020

Learning Objectives

After completing this activity, you should be better able to:

- Implement evidence-based strategies to manage mood disorders during pregnancy
- Improve diagnosis and treatment of mood disorders during the postpartum period

Accreditation and Credit Designation Statements

The Neuroscience Education Institute (NEI) is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

NEI designates this enduring material for a maximum of 1.0 *AMA PRA Category 1 Credit*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

The American Society for the Advancement of Pharmacotherapy (ASAP), Division 55 of the American Psychological Association, is approved by the American Psychological Association to sponsor continuing education for psychologists. ASAP maintains responsibility for this program and its content.

The American Society for the Advancement of Pharmacotherapy designates this program for 1.0 CE credit for psychologists.

Nurses and *Physician Assistants:* for all of your CE requirements for recertification, the ANCC and NCCPA will accept *AMA PRA Category 1 Credits*™ from organizations accredited by the ACCME. The content of this activity pertains to pharmacology and is worth 1.0 continuing education hour of pharmacotherapeutics.

Instructions for Optional Posttest and CME Credit

The estimated time for completion of this activity is 60 minutes. There is no posttest fee nor fee for CME credits.

1. Read the article
2. Complete the posttest and evaluation, available only online at www.neiglobal.com/CME (under "CNS Spectrums")
3. Print your certificate (passing score = 70% or higher)

Questions? call 888-535-5600, or email CustomerService@neiglobal.com

Peer Review

This content has been peer reviewed by a clinical PharmD specializing in women's health and psychopharmacology & behavioral health to ensure the scientific accuracy and medical relevance of information presented and its independence from commercial bias. NEI takes responsibility for the content, quality, and scientific integrity of this CME activity.

Disclosures

All individuals in a position to influence or control content are required to disclose any financial relationships. Although potential conflicts of interest are identified and resolved prior to the activity being presented, it remains for the participant to determine whether outside interests reflect a possible bias in either the exposition or the conclusions presented.

Disclosed financial relationships with conflicts of interest have been reviewed by the NEI CME Advisory Board Chair and resolved.

Authors

Michael Thomson, MD, is in the Department of Psychiatry at Western University in London, ON, Canada. Dr. Thomson has no financial relationships to disclose.

Verinder Sharma, MBBS, FRCPC, is a professor in the Departments of Psychiatry and of Obstetrics & Gynaecology at Western University in London, ON, Canada, and a consultant psychiatrist at the Perinatal Clinic in the Parkwood Institute at St. Joseph's Health Care London in London, ON, Canada. Dr. Sharma receives research support from Assurex, Neurocrine, Stanley Medical Research, and Sunovion.

No writing assistance was utilized in the production of this article.

CNS Spectrums Peer Review

All CME articles are peer reviewed in accordance with the strict standards of *CNS Spectrums* and in accordance with requirements and recommendations of the International Committee of Medical Journal Editors. The Editorial policies of the journal *CNS Spectrums* and peer review of all articles that appear in the journal is managed independently by Cambridge University Press and no financial relationship exists between the CME provider and Cambridge for this service.

Additional Peer Reviewer

Patrick R. Finley, PharmD, BCPP, is a professor of clinical pharmacy (in psychopharmacology and

behavioral health) in the department of clinical pharmacy at the University of California, San Francisco School of Pharmacy in San Francisco, CA. Dr. Finley has no financial relationships to disclose.

The **Content Editor** and **Planning Committee** have no financial relationships to disclose.

Disclosure of Off-Label Use

This educational activity may include discussion of unlabeled and/or investigational uses of agents that are not currently labeled for such use by the FDA. Please consult the product prescribing information for full disclosure of labeled uses.

Cultural and Linguistic Competency

A variety of resources addressing cultural and linguistic competency can be found at this link: www.neiglobal.com/go/cmeregs

Provider

This activity is provided by NEI. Additionally provided by ASAP.

Acknowledgment of Financial Support

This activity is supported by an unrestricted educational grant from Sage Therapeutics.

CNS Spectrums (2017), **22**, 52–63.
doi:10.1017/S1092852917000852

REVIEW ARTICLE

Between a rock-a-bye and a hard place: mood disorders during the peripartum period

Michael Thomson,[1] *and Verinder Sharma*[1,2]*

[1] Department of Psychiatry, Western University, London, Ontario, Canada
[2] Department of Obstetrics and Gynaecology, Western University, London, Ontario, Canada

Mood disorders including major depressive disorder and bipolar disorder are common during and after pregnancy. Timely identification and appropriate management of mood episodes is essential to maximize maternal well-being and minimize adverse outcomes. Failure to do so results in maternal suffering and impaired child bonding, and has the potential for devastating outcomes including suicide and infanticide. Women are routinely screened for unipolar depression during or after pregnancy but not for bipolar disorder, in spite of the fact that childbirth is associated with a major risk for onset or exacerbation of bipolar disorder. Delays in detection as well as misdiagnosis of bipolar disorder as major depressive disorder may put women at risk of many adverse consequences, including symptom exacerbation, psychiatric hospitalization, and suicide. A thorough psychiatric assessment is necessary to establish diagnosis, to address safety issues, and to formulate a treatment plan. Treatment of mood disorders during pregnancy is complicated by the potential risks of fetal exposure to psychotropic medications, and the use of these medications during the postpartum period may result in infant medication exposure through breastmilk. These risks of psychotropic medication exposure must be weighed against the risk of untreated mood disorders. This review will discuss the pathophysiology, epidemiology, diagnosis, and treatment of mood disorders during pregnancy and the postpartum period. Screening tools that can be used in the primary care and obstetrics settings to assist in identifying women with peripartum mood disorders will also be discussed.

Received 16 October 2017; Accepted 22 November 2017

Key words: Antenatal, bipolar, depression, peripartum, postpartum.

Introduction

Depression is the most common cause of disability worldwide, and there is a propensity for first presentations of mood disorders during the reproductive years in women.[1] Despite increasing public education and awareness of peripartum mood disorders, particularly postpartum depression, they remain underdiagnosed and undertreated. Some studies have suggested that the prevalence of depression in the postpartum period does not vary from the age-matched female population. Yet, the rates of mood disorder identification and treatment during this time remain low.[2] The reasons for this are probably numerous and complex. Often symptoms of peripartum mood disorders, such as fatigue and sleep disturbance, overlap with normal experiences of pregnancy and postpartum. As such, they may be dismissed despite being part of an underlying mood disorder. The identification of postpartum depressive episodes is made even more difficult by the overlap of many symptoms with "the baby blues," which are transient depressive symptoms considered to be a normal part of the postpartum period in many women.[3]

Inconsistency in defining the peripartum period has also been a source of confusion. The *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition (DSM-5) allows for the use of a specifier "with peripartum onset," which can be used when major depressive, hypomanic, or manic episodes onset during pregnancy or within the first 4 weeks postpartum. Some experts believe that expanding the peripartum period to 1 year following delivery would help identify the larger population of women at risk for postpartum mood disorders. Recent epidemiological data from Canada determined that the average time of antenatal suicide was at 5 months gestation and the average time of postpartum suicide was

* Address for correspondence: Dr. Verinder Sharma, Department of Psychiatry and Obstetrics and Gynaecology, Western University, London, Ontario, Canada.
(Email: vsharma@uwo.ca)

This activity is supported by an unrestricted educational grant from Sage Therapeutics.

at 7.5 months postpartum. The same study also identified that suicides in peripartum women are often by highly lethal methods, including hanging (33.3%) or jumping from heights (19.6%).[4] Limiting the peripartum period to 1-month duration may increase the risk of clinicians failing to identify women at higher risk for suicide.

Pathophysiology

Despite their high prevalence rates, the pathophysiology of peripartum mood disorders remains poorly understood. Likewise, it is unknown if they have different etiologies from non-peripartum mood disorders. There are likely multiple factors contributing to the increased risk for episodes of mood disorders in the postpartum period, including inflammatory, hormonal, and sleep-related changes.[5] Physiological alterations and medical conditions associated with pregnancy and postpartum, including anemia,[6] changes in thyroid hormones,[7] and alterations in serum vitamin D concentrations[8] may also contribute. Discontinuing medications prior to conception and during pregnancy is likely a factor in many cases of relapse.[9] The hormonal changes of pregnancy and postpartum are likely contributory to the differences observed in peripartum mood disorders versus other time points.[10] However, the evidence associating changes in estrogen and progesterone to postpartum depression has largely been limited to a small study of 8 women. In this study, women with a history of postpartum depression had a much higher rate of depressive symptom recurrence after being exposed to supraphysiologic doses of estrogen and progesterone which were then discontinued over 4 weeks. Five of the 8 women with a history of postpartum depression experienced increased depressive symptoms while none of the women in the control group did.[11] Although hormonal therapies are not part of the routine treatment for perinatal mood disorders, 2 studies, one of which was a randomized placebo-controlled trial, demonstrated improvements in depressive symptoms after estrogen was administered to women with postpartum depression.[12,13] A later study comparing the use of transdermal estrogen to sertraline and placebo for the treatment of postpartum depression was stopped after it was determined that the estradiol levels were not significantly different between the 3 treatment groups.[14] There is also ongoing investigation of brexanolone, an allopregnanolone formulation, which quickly and dramatically reduced symptoms of postpartum depression in a phase two clinical trial.[15]

Principles of Identifying Peripartum Mood Disorders

Given the high prevalence of peripartum mood disorders and the reluctance many women have in reporting depressive symptoms, some organizations have advised universal depression screening during the peripartum.[16,17] The American College of Gynecology and Obstetrics has recommended that universal peripartum screening be done using a validated screening instrument and that positive screens be followed up with effective treatment or referral to appropriate resources.[17] Validated questionnaires can be of great assistance in identifying peripartum mood disorders and tracking the illness course. The most frequently used and best studied tool is the Edinburgh Postnatal Depression Screen (EPDS). It is important to note that this is not a diagnostic tool, but rather a screening tool designed to identify women who should be further assessed for depression. The EPDS is a self-completed questionnaire that takes less than 5 minutes to complete and can easily be administered in various treatment settings. It has been validated for both antenatal and postpartum use. A pooled analysis by the US Preventative Services Task Force using the English-language EPDS with a cut-off score of 13 showed a sensitivity ranging from 67–100% and a specificity ranging from 87–100%. The task force also showed a 28–59% reduction in the risk of depression at 3 to 5 months follow-up after involvement of postpartum women in programs screening for depression, with or without treatment.[16] The EPDS was designed to avoid questions that may result in frequent false positives during the postpartum, eg, inquiring about fatigue, impaired sleep, or anhedonia. Many studies have used a score of ≥10/30 as a positive screen for "possible depression" and a score of ≥13/30 as a positive screen for "probable depression." A score of ≥20/30 has frequently been used as an indication of severe depression.

There is an increasing body of evidence showing that the postpartum period is a high-risk time for both first presentations and relapses of bipolar disorders.[18] The chronological overlap of the ages where bipolar disorder often first presents with the reproductive years in women is likely a contributory factor. The rate of first psychiatric hospitalization in women with bipolar disorder is increased 23-fold in the first postpartum month.[19] This high rate of bipolarity complicates the diagnosis of postpartum depression, as bipolar disorder most commonly presents as a major depressive episode (MDE).[20] In the Bipolar Disorders: Improving Diagnosis, Guidance and Education (BRIDGE) study, depending on the diagnostic criteria used, 15–50% of women who had a first MDE onset within 4 weeks after childbirth had evidence of bipolarity. This was significantly higher than women with a non-postpartum first episode MDE (5–37% rate of bipolarity) when *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision (DSM-IV-TR) criteria or the bipolar specifier were used, but not when Hypomania Checklist (HCL-32) criteria was used.[21] Clinical features suggestive of bipolarity include atypical antidepressant response, a history of brief depressive episodes, and episode onset within the first 14 days postpartum. These features are summarized in Table 1.

Upon identifying a MDE, it is important to elicit any past history of hypomanic, manic, or mixed episodes. It is also important to be judicious in the use of antidepressant medications, as their use in cases with an underlying bipolar disorder may induce mixed episodes. These are often more treatment-resistant and can have higher risks of suicide.[22–24] As bipolar disorder is highly heritable, obtaining a family psychiatric history, particularly of first-degree relatives, is vital. Screening tools can also be used to help assess for a potential bipolar disorder. Sharma and Xie[25] validated the Mood Disorders Questionnaire (MDQ) for use in the postpartum period. They demonstrated a sensitivity of 87.72% and specificity of 85.29% for the MDQ in identifying bipolar disorder when the supplementary questions were excluded. A positive MDQ indicates a possible bipolar spectrum disorder requiring further evaluation through psychiatric assessment. This screening tool has shown to be useful in identifying women at high risk of bipolar disorder or mixed depression when used in the primary care setting.[26] A diagnosis of MDD with mixed features should be considered in cases where both the EPDS and MDQ are positive but psychiatric assessment does not identify a bipolar disorder. The diagnostic algorithm presented in Figure 1 shows a potential pathway that can be followed in the screening and diagnosis of postpartum mood disorders. Bipolar disorder screening should be universal prior to initiation of antidepressant medication in any clinical setting.[27] Women with a positive MDQ screen should be referred for psychiatric assessment and treatment.

TABLE 1. Features suggestive of bipolarity in postpartum depression

Onset of depression in the early postpartum, especially within the first 14 days[18,81]
Psychiatric hospitalization required postpartum[18]
Current episode ≤1 month in duration[103]
Mixed features[104,105]
Psychotic symptoms[105]
≥4 previous depressive episodes[103]
Brief depressive episodes[105]
Age <30 at onset of psychiatric symptoms[103]
Seasonal fluctuations in depressive symptoms[103]
Atypical antidepressant response: precipitation of mixed, hypomanic, or manic episodes; rapid antidepressant response; poor antidepressant response; loss of antidepressant response[103]
Neurotic personality trait[106]
Family history of bipolar disorder in a first-degree relative[103]

Studies have suggested that only 40% of depressive episodes identified during the postpartum period actually had postpartum onset.[28] As such, it is important to screen women during the antenatal period and if treatment is not initiated during pregnancy, to reassess the patient again postpartum. Although there may be differences in prognoses and treatment responses between pre-pregnancy, antenatal, and postpartum onset MDD episodes, this has yet to be clearly shown in the literature. For the purposes of this article, the term antenatal will be used to reference any episodes identified during the pregnancy regardless of pregnancy or pre-pregnancy onset. Likewise, postpartum will be used to reference any episodes identified in the first year following childbirth, even if onset was during pregnancy or pre-pregnancy.

Patients with postpartum depression must be screened for psychosis, which in most cases is a manifestation of bipolar disorder.[29] However, schizophrenia, major depressive disorder, substance misuse, and medical conditions

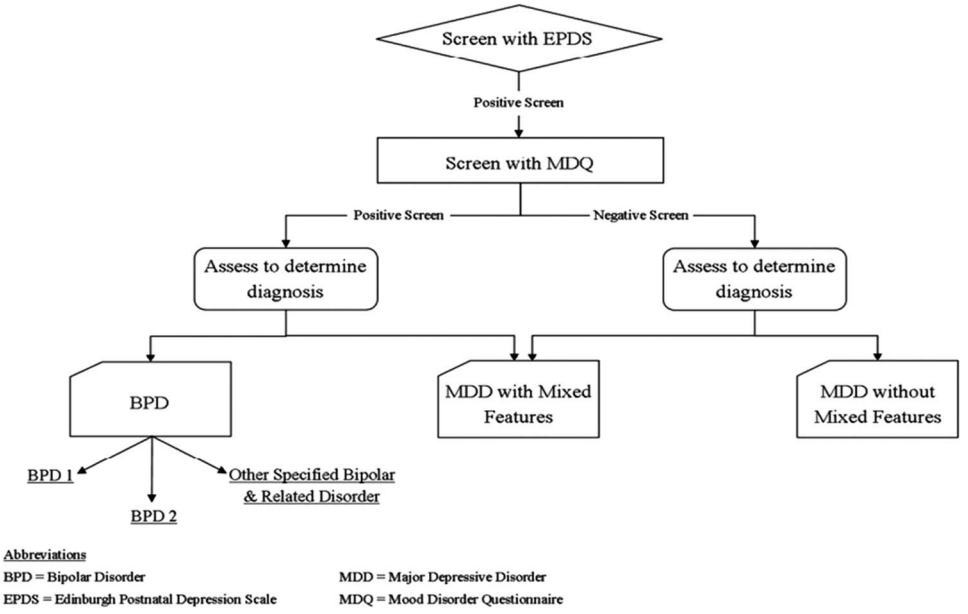

FIGURE 1. Diagnostic algorithm for postpartum depression.

may also cause postpartum psychosis. This condition is seen in 0.1% of postpartum women and is considered a psychiatric emergency.[30,31]

Principles of Treatment in Peripartum Mood Disorders

A wait and watch approach may be appropriate in managing some episodes of postpartum depression, particularly those with early postpartum onset. However, urgent intervention is usually required with mixed episodes or when psychotic features are present. If patients have psychotic features, are at significant risk for suicide, or have significant functional impairment, then psychiatric hospitalization may be required. Otherwise, an appropriate period of observation may assist in differentiating a potential mood disorder from the baby blues or transient distress associated with pregnancy or postpartum. This also allows for further monitoring for symptoms which could be suggestive of bipolarity (Table 1). Should a wait and watch approach be taken, the woman and her supports should be educated on how they can access urgent psychiatric follow-up should her symptoms worsen.

When a woman has opted not to breastfeed, treatment can follow guidelines that have been written for the general mood disorders population, such as those published by the Canadian Network for Mood and Anxiety Treatments (CANMAT) or National Institute for Clinical Excellence (NICE).[32–34] However, the woman's plans for future pregnancies and the use of contraceptive methods should be discussed, as some medications, especially valproate and carbamazepine, have significant teratogenic effects that may impact a future pregnancy.[35]

It is important to have a thorough discussion of the risks and benefits associated with psychotropic medications prior to their use in pregnancy. Should medications be used, those that the women previously responded to should be given strong consideration while also considering the medication's safety profile in pregnancy and compatibility with breastfeeding. Where possible, pharmacotherapy should be limited to a single medication. Higher doses of a single medication are usually safer to the fetus or breastfeeding infant than using lower doses of multiple medications.[33] Clinicians should also be mindful that higher doses may be required during pregnancy to compensate for pharmacokinetic changes, including an increased volume of distribution and alterations in metabolizing enzymes. Reduction in dosage may also be required in the immediate postpartum once these pregnancy-associated pharmacokinetic changes reverse.[36]

A thorough discussion of medication safety in pregnancy and breastfeeding is beyond the scope of this article, but it is an important area of understanding for clinicians. This information is reviewed in the consensus paper by the British Association for Psychopharmacology that summarizes the risks and benefits of psychotropic medication use during the peripartum period.[37] Given the increased use of psychotropic medications in the general population, women are increasingly seeking consultation on the use of psychotropic medications both before conception and after a pregnancy has been identified.[38] It is also vital to compassionately address the stigma that many women face if they have been diagnosed with a psychiatric disorder or are contemplating the use of psychotropic medications. Many women will opt to discontinue medications during the peripartum. This may be appropriate in some cases, but it is best done after completing a thorough risk assessment considering the past psychiatric history, available social supports, access to psychotherapy, and access to follow-up care. Having a thorough knowledge of the woman's past psychiatric history is important to determine the indication for the prescribed medication, to assess current symptomatic burden, and to help quantify the risks of relapse if medication is discontinued. This also provides an opportunity to assess for psychiatric comorbidities, which occur in two-thirds of peripartum women with MDD.[39] Antenatal anxiety is particularly common, with prevalence rates exceeding those of antenatal depressive symptoms.[40] Additionally, antenatal generalized anxiety disorder is an independent predictor of postpartum depression.[41] Tapering or discontinuing medication with symptom monitoring may be a reasonable treatment option when past mood disorder episodes have been infrequent, mild to moderate in severity, and have not included suicidality. It is important to determine the patient's preferences for treatment but also to counsel her that discontinuing psychotropic medications can increase the risk of a relapse, especially in women with a history of peripartum mood disorders.[42]

Regardless of the etiology, treatment of postpartum psychosis generally involves the use of antipsychotic medications, but may also involve mood stabilizers, benzodiazepines, or electroconvulsive therapy (ECT). Inpatient hospitalization is usually required to minimize the risk of adverse outcomes including infanticide.[31]

Management of Antenatal Major Depressive Disorder

Major depressive episodes comprise the majority of mood episodes encountered during pregnancy.[20] For episodes of mild to moderate severity, psychotherapy should be considered the first-line treatment option.[33,43] Unfortunately, for many women, access to psychotherapy may be limited by financial concerns, a lack of available practitioners, and inadequate available time. The psychotherapy modalities best supported by evidence are cognitive behavioral therapy (CBT) and interpersonal

therapy (IPT). Both of these modalities are supported by positive randomized controlled trials (RCTs) showing small to medium effect size.[44,45] The use of psychotherapy avoids fetal medication exposure and has a very low risk of adverse effects. Other treatment options with some, but limited, supportive evidence include bright light therapy, exercise, vitamin D, omega-3 oils, folic acid, and supportive psychotherapy.[46] These treatment options can be considered in women who wish to avoid the use of psychotropic medications and can reliably access follow-up care should their symptoms worsen.

Antidepressant medication is the first-line treatment for severe antenatal major depressive disorder. Psychotherapy may also be utilized but is best used as augmentation of medication in women who remain sufficiently functional to engage in therapy. However, there are no existing studies that show efficacy for psychotherapy augmentation in antenatal depression. Given this paucity of data, it is reasonable to extrapolate findings from non-peripartum MDD which have shown benefit from the combination of psychotherapy and antidepressant medication. Psychotherapy as a monotherapy treatment may be an option in severe MDD episodes for women who are opposed to the use of medication, but it should be used in combination with psychotropic medications in women with suicidality, significant functional impairment, or psychotic features.

There are no comparative studies on the efficacy of different antidepressants in treating antenatal depression. The use of antidepressant medications has been supported by multiple treatment guidelines when the risk of untreated depression is greater than the risks of fetal medication exposure and medication side effects.[33,43] There are known risks associated with antidepressant medications that must be carefully considered before their use in pregnancy. The fetal safety data are best established for selective serotonin reuptake inhibitor (SSRI) medications, but even among these medications, large studies and meta-analyses have differed in their findings of adverse outcomes. Some meta-analyses have shown a small increased risk of spontaneous abortion, whereas others did not. A systematic review and meta-analysis by Ross and Grigoriadis[47] showed a trend toward an increased risk of spontaneous abortion after SSRI exposure with an odds ratio of 1.47, which did not reach statistical significance (95% CI 0.99–2.17, P = 0.55). A recent review by Ornoy and Koren[48] summarized these studies and concluded that SSRIs do not seem to increase the rate of miscarriage. While previous studies suggested that pregnancy exposure to SSRIs was associated with higher rates of pre-term birth and low birth weight,[49] this was not found in a larger study by Malm *et al*,[50] which used groups unexposed to SSRIs both with and without psychiatric illness as comparators. In this study women treated with SSRIs had a lower risk of preterm (32–36 weeks, adjusted OR 0.84, 95% CI 0.74–0.96) and very preterm (<32 weeks, adjusted OR 0.52, 95% CI 0.37–0.74) births compared to untreated women with psychiatric illness. Rates of preterm births did not significantly differ between the SSRI-exposed pregnancies and the healthy unexposed group after adjustment. In the same study, offspring exposed to SSRIs had higher rates of low Apgar scores and monitoring in a neonatal care unit compared to both the health controls and the untreated women with psychiatric disorders.[50] A large cohort study of 3.8 million pregnancies showed a slightly increased rate of persistent pulmonary hypertension (PPHN) in fetuses when SSRIs were prescribed late in the pregnancy (31.5/100,000) compared to pregnancies with non-SSRI antidepressant exposure (29.1/100,000) and fetuses from unexposed pregnancies (20.8/100,000). The adjusted OR for PPHN was 1.12 (95% CI 0.95–1.31) in pregnancies exposed to SSRIs.[51] It is felt that SSRI medications are not major teratogens, as the overall rates of congenital anomalies in SSRI-exposed fetuses have been similar to unexposed fetuses, except for a small increase in cardiac anomalies.[48] Recent research has also shown an association between antenatal antidepressant use and the development of psychiatric disorders in the exposed offspring.[52] However, it is possible that the severity of maternal illness is the predominate causal factor for this rather than antidepressant exposure.

Although efficacious in non-antenatal MDD and frequently used to treat MDD in women who later become pregnant, there are no RCTs that have examined the efficacy of serotonin and norepinephrine reuptake inhibitors (SNRIs), bupropion, or mirtazapine in treating antenatal depression. Most studies of these medications have suggested low rates of teratogenicity, but there are much fewer safety data available for these medications compared to the SSRIs.[53–55] A recent study by Newport *et al*[56] showed an increased prevalence of hypertensive disorders of pregnancy with SNRI exposure after 20 weeks of gestation (OR 2.57, 95% CI 1.34–4.93). Early pregnancy use of bupropion was associated with a small increase in the risk of left outflow tract cardiac defects (adjusted odds ratio 2.6, 95% CI 1.2–5.7),[57] but this finding was not seen in a later cohort study.[58] A systematic review by Smit *et al*[54] of mirtazapine use in pregnancy concluded that there may be an association between mirtazapine use and spontaneous abortion, but also indicated that underlying psychiatric illness may be a confounder.

When a patient has not previously shown response to another antidepressant, sertraline is recommended as a first-line medication. While most studies analyzing the safety of antidepressants during pregnancy have looked at the SSRI class as a whole, sertraline has been one of the most frequently used medications in these analyses.[59] It has also shown to have the lowest ratio of umbilical cord serum concentration to maternal serum concentration of the SSRIs. This suggests that sertraline may have

less fetal medication exposure than the other SSRIs.[60] Other positive attributes of sertraline are good tolerability, a wide therapeutic dosage range, and a large amount of data demonstrating breastfeeding compatibility.[61] For women who do not tolerate sertraline, escitalopram is a reasonable alternative, as it is generally well tolerated and has a flexible dosing range. Most studies have shown that tricyclic antidepressants have low rates of associated congenital anomalies.[62] Monoamine oxidase inhibitors are generally contraindicated in pregnancy given the risk of interaction with various medications, especially anesthetic agents.[43] There are no established standards on how many medications of a class should be trialed before switching to another medication class in treating antenatal depression.

Unfortunately, there is little literature and no studies available to guide management of treatment-resistant antenatal MDD. Discussion of medication combinations and augmentation strategies for antenatal depression and the use of neuromodulation through electroconvulsive therapy, repetitive transcranial magnetic stimulation, and deep brain stimulation are beyond the scope of this review but can be further read about in a 2013 review by Robakis and Williams.[63]

Management of Postpartum Major Depressive Disorder

Postpartum MDD accounts for 70% of MDEs in the postpartum period.[28,64] Many aspects of treating postpartum MDD remain the same as in the treatment of antenatal depression. For mild to moderate depressive episodes, CBT and IPT remain first-line treatment options.[43] However, many women find it difficult to engage in therapy given the high demands of an infant and financial difficulties that young families often face. Internet- and telephone-based CBT are additional psychotherapy options that are supported by randomized controlled trials for treating postpartum depressive symptoms and are often easier for women to access than conventional psychotherapy.[65–68] Alternatively, treatment with antidepressant medications may be appropriate in women who are not interested in psychotherapy. Antidepressant medications remain the mainstay of treatment in cases of severe postpartum MDD. Psychotherapy can be used as an augmentation strategy to medications in treating severe postpartum MDD, but this combination has not been supported by research findings. To date, all of the RCTs that have examined the combination of antidepressants with psychotherapy in postpartum depression have been negative. These included trials that showed that there was no benefit from adding CBT to either fluoxetine or paroxetine.[69,70] Another trial showed no benefit in the use of sertraline compared to placebo when combined with brief dynamic psychotherapy.[71] However, there is evidence for increased efficacy of combined pharmacotherapy with psychotherapy in the general MDD population.[72]

SSRI medications have the largest amount of data supporting their use in postpartum episodes of MDD.[73] However, the use of antidepressants in breastfeeding women requires a careful discussion of the benefits versus the potential risks of the medication to the breastfeeding infant. In general, no antidepressant medications are contraindicated in breastfeeding, with the exception of MAOIs. There is also consensus that the breastfeeding exposure to most antidepressant medications is much less, potentially up to 10-fold, than in utero exposure if the same medication was used during pregnancy.[74,75] Most antidepressant medications maintain low relative infant doses (RID), defined by the ratio of the serum drug concentration of the infant compared to the mother. Studies have shown very low RIDs for sertraline and paroxetine, often with undetectable serum levels of the medication and its metabolites.[61] Among the SSRIs, fluoxetine tends to have a higher relative infant dose because of its long half-life.[75] When a woman has previously shown response to a particular antidepressant, it is generally recommended to restart that same antidepressant should pharmacotherapy be indicated, even if there are less breastfeeding safety data available.

Although antidepressants as a medication class are the mainstay of treatment for severe postpartum MDD, their overall efficacy is not well established. There have been numerous open trials that showed efficacy for different antidepressants, but meta-analyses of RCTs have shown mixed results. Two recent meta-analysis of antidepressant efficacy in postpartum MDD analyzed the same 6 RCTs. The systematic review by Sharma and Sommerdyk[76] did not find that antidepressants as a group showed efficacy in treating postpartum depression. However, the authors note that methodological limitations, including low recruitment rates resulting in small studies, may potentially explain this finding.[76] The systematic review by De Crescenzo *et al*[77] concluded that antidepressants appear to be efficacious and well tolerated in postpartum depression. However, this review also noted that the evidence does not clearly demonstrate that antidepressants are superior to other treatments.[77] The only antidepressants that have been supported by RCTs in the treatment of postpartum MDD are sertraline and fluoxetine, which each have 1 positive study. Not included in the above mentioned meta-analyses was a more recent positive study by Hantsoo *et al*[78] that showed response and remission rates of 59% and 53%, respectively, for sertraline versus 26% and 21%, respectively, for placebo after 6 weeks of treatment. An additional RCT showed a reduced recurrence of postpartum depression and a longer time to recurrence when sertraline was started in the immediate postpartum.[79] As it is supported by both these studies and a large

amount of breastfeeding safety data, sertraline is a first-line antidepressant in cases of postpartum depression where the woman has not previously shown robust response to another antidepressant.

Open-label studies have suggested efficacy for sertraline, escitalopram, fluoxetine, venlafaxine, and bupropion SR.[73] Usage of bupropion in breastfeeding women has received mixed support, as a case report suggested the possibility of increased infant seizure risk.[80] Bupropion may be a good treatment option in women who are not breastfeeding, especially those with atypical depressive symptoms and without significant comorbid anxiety. Monoamine oxidase inhibitors should be avoided, except for rare and treatment-resistant cases, given their risk of interactions with food and medications.

There is a paucity of literature available to guide management of treatment-resistant postpartum depression. Given this lack of information, guidelines for treatment-resistant depression in the general MDD population, such as CANMAT, can be followed.[32] Based on results from the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial involving the general MDD population, if an initial trial with a SSRI medication is ineffective, it is reasonable to try either another SSRI medication or an antidepressant of another medication class. It is also important to monitor for a potential exacerbation of symptoms or the emergence of mixed symptoms, as treatment resistance can be suggestive of an underlying bipolar disorder, especially with postpartum onset depression.[81] The only medication with supportive evidence for augmentation in treatment-resistant postpartum MDD is aripiprazole, which showed efficacy in a small open-label trial.[82]

Management of Antenatal Bipolar Disorder

Women with bipolar disorder have a high risk of experiencing a relapse during pregnancy. Most commonly these relapses take the form of MDEs, but they can alternatively be hypomanic, manic, or mixed episodes.[83] A meta-analysis by Wesseloo *et al*[9] including 5,700 deliveries from 4,023 women previously diagnosed with bipolar disorder showed an overall relapse rate of 37%. There were no significant differences in the relapse rates between women with bipolar I and bipolar II disorders. Those who remained on prophylactic medications had a much lower relapse rate compared to women who discontinued their medication (23% versus 65%, $p = 0.001$).[9] This risk of relapse must be weighed against the significant fetal risk associated with some mood stabilizing medications. Ideally women with bipolar disorder would be stabilized for a period of 6 months or longer prior to conception, but given that up to two-thirds of pregnancies in women with bipolar disorder are unplanned, this is frequently not the case.[84] As a result, it is very important to obtain a thorough past psychiatric history, especially with respect to past peripartum course, to determine the severity of the bipolar illness and to help estimate the potential risk of a relapse. It is also vital to discuss how the woman feels about the use of medications for prophylactic or maintenance treatment during pregnancy and to discuss their risks and benefits. Discontinuation of mood stabilizing medications is very common, as both women and practitioners are often concerned about causing fetal harm. However, any alteration in psychotropic medication requires close follow-up to monitor for symptom relapse. Both patients and involved supports should be educated on the potential signs of relapse so that any deteriorations can be quickly identified.

Most guidelines strongly caution against the use of valproate in pregnancy and some deem it contraindicated. The UK NICE guidelines recommend avoidance of valproate for the treatment of mental disorders in women of reproductive age, and also that carbamazepine not be used in women who are pregnant, breastfeeding, or planning to have a baby.[33] Additionally, a study by Wisner *et al*[85] demonstrated that valproate was no more effective than monitoring without medication in preventing bipolar depression relapse.[85] Ideally, euthymic women on valproate planning to become pregnant are identified before conception so that they can be changed to a maintenance medication with less teratogenicity. In cases where women become pregnant while on valproate, it is usually best to discontinue the medication and switch to an alternative mood stabilizer with less fetal risk. It is also recommended to prescribe a daily dose of 1–4 mg of folic acid for the first trimester to potentially reduce the risk of neural tube defects when women have taken antiepileptic medications in pregnancy. This recommendation has little data supporting it, but theoretically it may reduce the risk of fetal neural tube defects. A study of 311 6-year-old children from mothers with epilepsy taking antiepileptics showed that children exposed to periconceptional folate had higher mean IQs compared to children from pregnancies that were not supplemented with folate (108 vs 101). However, in this study folate exposure was determined by retrospective maternal interview and the authors caution that the findings may have been influenced by confounding factors.[86]

Lamotrigine has shown efficacy as a maintenance treatment in bipolar disorder in the non-peripartum population.[34] A prospective observational trial showed that euthymic pregnant women with bipolar disorder relapsed less frequently when they remained on lamotrigine maintenance compared to pregnant women who discontinued all of their mood stabilizing medications (30% versus 100%).[87] Lamotrigine is thought to be non-teratogenic and a mood stabilizer with one of the best safety profiles in pregnancy.[88] However, serum lamotrigine levels can vary

substantially during pregnancy and the postpartum, requiring frequent monitoring.[33] If women do not respond to or tolerate lamotrigine, quetiapine is an alternative treatment with efficacy in bipolar disorder maintenance in non-peripartum populations and it is not believed to be a major teratogen.[34,89]

Most studies of prophylactic treatment of bipolar disorder in pregnancy have used lithium. These studies have shown lithium to be efficacious in preventing bipolar depression relapses. An open label trial by Rosso *et al*[90] showed its efficacy in preventing relapse in women with bipolar I disorder. Of the 18 pregnancies where lithium was continued, there was a relapse of mood episodes in only 17.7%. While there was no comparison group in this study, a relapse rate of 17.7% is much lower than the 65% relapse rate of women who discontinued mood stabilizing medication in the study by Wesseloo *et al*.[9] However, the first trimester use of lithium has been associated with the development of Ebstein's anomaly, a congenital cardiac defect of the tricuspid valve. This risk was thought to be 400 times higher than in the general population in original studies.[91] More recent data have suggested that this risk was most likely over-estimated. A recent retrospective study showed a rate of cardiac outflow obstructions in babies exposed to lithium of 0.6% versus 0.2% in those not exposed. Lithium may increase the overall risk of congenital malformations by a factor of 2 (6.6% of exposed pregnancies).[33] A cohort study by Patorno *et al*[91] of 1.3 million pregnancies with 663 infants exposed to lithium showed an adjusted risk ratio of 1.65 for cardiac malformations in fetuses exposed to lithium. This decreased to 1.11 for daily doses less than 600 mg and increased to 3.22 for doses greater than 900 mg.[92] Lithium requires titration of doses based on serum levels and generally requires higher doses throughout pregnancy as glomerular filtration rate increases. There are mixed opinions on the compatibility of lithium with breastfeeding. Most of the recent guidelines are supportive of its use; however, lithium is known to achieve relatively high concentrations in breastmilk resulting in significant infant exposure.[93]

General recommendations for the treatment of acute antenatal bipolar depressive episodes do not vary from those used in maintenance treatment. Lamotrigine remains a good medication choice because of the low risk of teratogenicity seen in most studies and favorable side effect profile. Quetiapine is an alternative option in patients who have previously responded to it or do not respond to lamotrigine.

Although it is not supported by data specific to antenatal bipolar depression, there may be benefit in augmenting medication management with psychotherapies such as CBT and IPT. These therapy modalities have shown efficacy in treating bipolar depression in the general psychiatric population. In cases where women opt not to use medications, psychotherapies may help in preventing relapses of mood episodes.[34]

Antenatal manic episodes may best be managed by medications that differ from those used for bipolar maintenance treatment and bipolar depressive episodes. Lamotrigine's use is not well established in treating mania.[34] Lithium has shown high efficacy but has associated teratogenicity, and some clinicians feel that it is slower to elicit a response than antipsychotics. Often antipsychotics are used in treating manic episodes, with both first-generation and second-generation antipsychotics appearing efficacious. Similar to treating other peripartum mood disorder episodes, if a patient has previously responded well to a particular medication in treating manic episodes, then use of that same medication should be strongly considered. However, the use of valproate and carbamazepine are avoided in pregnancy except in very treatment-resistant cases. These medications should be reserved for cases where the episodes have been refractory to all other treatments and only used after careful discussion with the patient and her family. Haloperidol has shown efficacy in treating mania outside of the peripartum period and has not been associated with congenital anomalies.[94] The use of second-generation antipsychotics, such as olanzapine and risperidone, are alternative options, but these medications are also associated with metabolic side effects that can pose additional risks for adverse obstetrical outcomes. A thorough discussion of the risks associated with antipsychotic use in pregnancy can be found in the 2015 systematic review by Coughlin *et al*.[95]

Management of Postpartum Bipolar Disorder

Depressive episodes are the predominate form of bipolar disorder relapse during the postpartum. However, hypomanic, manic, and mixed episodes also happen at a higher rate in the postpartum, especially within the first month.[20] Given the high risk of postpartum relapse and the potentially devastating effects that accompany it, prophylactic treatment should be strongly considered. Although women who remain off medication throughout the pregnancy have a significantly higher rate of relapse, the initiation of prophylactic medications immediately prior to or following childbirth may ameliorate this risk. When prophylactic treatment was initiated immediately following delivery, the relapse rate was 29% compared to 65% in women who remained medication-free postpartum. The relapse rate of women who remained on prophylactic pharmacotherapy during pregnancy was the lowest at 23%.[9]

Most of the existing studies for prophylactic treatment of peripartum bipolar disorder have used lithium.[96,97] These studies have shown a significantly decreased risk

of relapse after lithium prophylaxis. As a result, lithium is a reasonable medication choice in women who are not planning on breastfeeding. The use of lithium is not contraindicated in breastfeeding women, but it appears to reach relatively high concentrations in breastmilk and some experts have cautioned against it. A systematic review by Uguz and Sharma[93] analyzed 26 cases of lithium use in breastfeeding and found that lithium had a milk to plasma concentration ratio of 0.53, an infant serum level of 0.16 mEq/L, and an infant to maternal serum concentration ratio of 0.24. The opinion of the authors was that there are no clear contraindications for lithium use during breastfeeding, but it should be reserved for situations where other options are not available.[93] Olanzapine was also shown to have efficacy in preventing postpartum psychosis and postpartum mood episodes in patients with bipolar disorder. In a small open-label study, 11 women treated with olanzapine, with or without a mood stabilizer, had a much lower relapse rate than 14 women who received either a mood stabilizer, an antidepressant, or no medication (18.2% versus 57.1%, respectively). Only 3 of the 11 women receiving olanzapine started the medication prior to childbirth.[98] Lamotrigine also has evidence in both maintenance and bipolar depression treatment in the non-peripartum population.[34] Although this medication is also known to attain relatively high concentrations in breastmilk, the consensus is that it is probably safe in women who are breastfeeding.[93]

To date, the only medication that has supportive evidence in treating acute postpartum bipolar depression is quetiapine. The evidence is limited to a single chart review by Sharma *et al*[99] involving 18 women with a diagnosis of bipolar I, bipolar II, or bipolar NOS. All of the women included in this study experienced an onset of depression within the first 4 weeks postpartum. After 8 weeks of treatment with quetiapine, 83% of the women were rated as "much" or "very much" improved. The median dose of quetiapine used was only 75 mg.[99] As this is the only study of acute treatment for bipolar mood episodes in the postpartum period, it is reasonable to follow existing treatment guidelines for the general bipolar disorder population if the patient is not breastfeeding. However, in accordance with the NICE guidelines, it is recommended to avoid the use of valproate, unless there has been minimal response to other treatment options, as another pregnancy may be considered or encountered during treatment.

No studies have focused on the treatment of hypomania and mania in the postpartum. Given this lack of information, treatment should follow existing guidelines developed for use in the general bipolar disorder population with additional consideration to breastfeeding compatibility where applicable. This will often involve the use of antipsychotic or mood stabilizing medications. The safety of mood stabilizing and second-generation antipsychotic medications in breastfeeding is summarized in systemic reviews by Uguz and Sharma.[93,100]

In treating postpartum bipolar disorder, the risks and benefits of breastfeeding should be discussed with the woman and her family. Although there are many established benefits to breastfeeding, the associated sleep disruptions may contribute to the mood disorder episodes.[101] Additionally, many mood stabilizing medications are sedating, which can potentially improve sleep but may make nighttime feedings harder. If possible, bottle feeding at night by the woman's partner or support can be beneficial to allow the woman to maintain a better sleeping schedule. In postpartum psychosis or bipolar disorder with psychotic features, the woman may be too disorganized to safely breastfeed, which must be reviewed on a case-by-case basis.

Conclusions

Peripartum mood disorders remain under-recognized and undertreated. Adding to this issue is the complexity of their management, as antenatal pharmacotherapy results in fetal exposure to medications and postpartum pharmacotherapy may result in infant medication exposure through breastmilk. Unfortunately, there is a paucity of literature to guide treatment decisions, especially with respect to treatment-resistant depression and the treatment of peripartum bipolar disorder. The need to balance the safety of medication exposures against the risk of untreated maternal illness is one of the reasons that peripartum mood disorders can be considered being "stuck between a rock and a hard place." Untreated peripartum mood disorders increase the risk of adverse obstetrical and child development outcomes, in addition to causing significant maternal suffering.[102]

Disclosures

Dr. Michael Thomson has nothing to disclose. Dr. Sharma reports grants from Neurocrine Biosciences, Stanley Medical Research Institute, Sunovion Pharmaceuticals, and Assurex Health, outside the submitted work.

REFERENCES:

1. Pedersen CB, Mors O, Bertelsen A, *et al*. A comprehensive nationwide study of the incidence rate and lifetime risk for treated mental disorders. *JAMA Psychiatry*. 2014; **71**(5): 573–581.
2. Gaynes BN, Gavin N, Meltzer-Brody S, *et al*. Perinatal depression: prevalence, screening accuracy, and screening outcomes. *Evid Rep Technol Assess (Summ)*. 2005;Feb(119): 1–8.
3. Misri S, Burgmann AJ. Postpartum mood disorders: recognizing the symptoms. *Can Fam Physician*. 1992; **38**: 2031–2036.
4. Grigoriadis S, Wilton SA, Kurdak PA, *et al*. Perinatal suicide in Ontario, Canada: a 15-year population-based study. *CMAJ*. 2017; 89(34): e1085–e1092.

5. Brummelte S, Galea LA. Postpartum depression: etiology, treatment and consequences for maternal care. *Horm Behav*. 2016; **77**: 153–166.
6. Eckerdal P, Kollia N, Lofblad J, *et al*. Delineating the association between heavy postpartum haemorrhage and postpartum depression. *PLoS One*. 2016; **11**(1): pe0144274.
7. Pedersen CB, Johnson JL, Sliva S, *et al*. Antenatal thyroid correlates of postpartum depression. *Psychoneuroendocrinology*. 2007; **32**(3): 235–245.
8. Gur EB, Genc M, Eskiciogiu F, *et al*. The effect of vitamin D level in pregnancy on postpartum depression. *Arch Womens Ment Health*. 2015; **18**(2): 263–264.
9. Wesseloo R, Kamperman AM, Munk-Olsen T, *et al*. Risk of postpartum relapse in bipolar disorder and postpartum psychosis: a systematic review and meta-analysis. *Am J Psychiatry*. 2016; **173** (2): 117–127.
10. Hendrick V, Altshuler LL, Suri R. Hormonal changes in the postpartum and implications for postpartum depression. *Psychosomatics*. 1998; **39**(2): 93–101.
11. Bloch M, Schmidt PJ, Danaceau M, *et al*. Effects of gonadal steroids in women with a history of postpartum depression. *Am J Psychiatry*. 2000; **157**(6): 924–930.
12. Ahokas A, Kaukoranta J, Wahlbeck K, Alto M. Estrogen deficiency in severe postpartum depression: successful treatment with sublingual physiologic 17beta-estradiol: a preliminary study. *J Clin Psychiatry*. 2001; **62**(5): 332–336.
13. Gregoire AJ, Kumar R, Everitt B, *et al*. Transdermal oestrogen for treatment of severe postnatal depression. *Lancet*. 1996; **347** (9006): 930–933.
14. Wisner KL, Sit DK, Moses-Kolko EL, *et al*. Transdermal estradiol treatment for postpartum depression: a pilot, randomized trial. *J Clin Psychopharmacol*. 2015; **35**(4): 389–395.
15. Kanes S, Colquhoun H, Gunduz-Bruce H, *et al*. Brexanolone (SAGE-547 injection) in post-partum depression: a randomised controlled trial. *Lancet*. 2017; **390**(10093): 480–489.
16. O'Connor E, Rossom RC, Henninger M, *et al*. *Screening for depression in adults: an updated systematic evidence review for the U.S. Preventive Services Task Force. Report No.: 14-05208-EF-1*. Rockville, MD: Agency for Healthcare Research and Quality; 2016.
17. Committee on Obstetric Practice. The American College of Obstetricians and Gynecologists Committee Opinion no. 630. Screening for perinatal depression. *Obstet Gynecol*. 2015; **125**(5): 1268–1271.
18. Munk-Olsen T, Laursen TM, Meltzer-Brody S, *et al*. Psychiatric disorders with postpartum onset: possible early manifestations of bipolar affective disorders. *Arch Gen Psychiatry*. 2012; **69**(4): 428–434.
19. Munk-Olsen T, Laursen TM, Pedersen CB, *et al*. New parents and mental disorders: a population-based register study. *JAMA*. 2006; **296**(21): 2582–2589.
20. Viguera AC, Tondo L, Koukopoulos AE, *et al*. Episodes of mood disorders in 2,252 pregnancies and postpartum periods. *Am J Psychiatry*. 2011; **168**(11): 1179–1185.
21. Azorin JM, Angst J, Gamma A, *et al*. Identifying features of bipolarity in patients with first-episode postpartum depression: findings from the international BRIDGE study. *J Affect Disord*. 2012; **136**(3): 710–715.
22. Rihmer Z, Gonda X. Antidepressant-resistant depression and antidepressant-associated suicidal behaviour: the role of underlying bipolarity. *Depress Res Treat*. 2011; **2011**: 906462.
23. Sharma V. A cautionary note on the use of antidepressants in postpartum depression. *Bipolar Disord.* 2006; **8**(4): 411–414.
24. Seo HJ, Wang HR, Jun TY, *et al*. Factors related to suicidal behavior in patients with bipolar disorder: the effect of mixed features on suicidality. *Gen Hosp Psychiatry*. 2016; **39**: 91–96.
25. Sharma V, Xie B. Screening for postpartum bipolar disorder: validation of the Mood Disorder Questionnaire. *J Affect Disord*. 2011; **131**(1–3): 408–411.
26. Çelik SB, Bucaktepe GE, Uludağ A, Bulut İU, Erdem Ö, Altınbaş K. Screening mixed depression and bipolarity in the postpartum period at a primary health care center. *Compr Psychiatry*. 2016; **71**: 57–62.
27. Sharma V, Pope CJ. Pregnancy and bipolar disorder: a systematic review. *J Clin Psychiatry*. 2012; **73**(11): 1447–1455.
28. Wisner KL, Sit DKY, McShea MC, *et al*. Onset timing, thoughts of self-harm, and diagnoses in postpartum women with screen-positive depression findings. *JAMA Psychiatry*. 2013; **70**(5): 490–498.
29. Chaudron LH, Pies RW. The relationship between postpartum psychosis and bipolar disorder: a review. *J Clin Psychiatry*. 2003; **64**(11): 1284–1292.
30. Brockington I. Postpartum psychiatric disorders. *Lancet*. 2004; **363**(9405): 303–310.
31. Spinelli MG. Postpartum psychosis: detection of risk and management. *Am J. Psychiatry*. 2009; **166**(4): 405–408.
32. Kennedy SH, Lam RW, McIntyre RS, *et al*. Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 clinical guidelines for the management of adults with major depressive disorder: section 3. pharmacological treatments. *Can J Psychiatry*. 2016; **61** (9): 540–560.
33. National Institute for Health and Care Excellence (NICE). Antenatal and postnatal mental health. 2016; https://www.nice.org.uk/guidance/qs115/resources/antenatal-and-postnatal-mental-health-75545299789765.
34. Yatham LN, Kennedy SH, Parikh SV, *et al*. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) collaborative update of CANMAT guidelines for the management of patients with bipolar disorder: update 2013. *Bipolar Disord*. 2013; **15**(1): 1–44.
35. Hernandez-Diaz S, Smith CR, Shen A, *et al*. Comparative safety of antiepileptic drugs during pregnancy. *Neurology*. 2012; **78**(21): 1692–1699.
36. Costantine MM. Physiologic and pharmacokinetic changes in pregnancy. *Front Pharmacol*. 2014; **5**: 65.
37. McAllister-Williams RH, Baldwin DS, Cantwell R, *et al*. British Association for Psychopharmacology consensus guidance on the use of psychotropic medication preconception, in pregnancy and postpartum 2017. *J Psychopharmacol*. 2017; **31**(5): 519–552.
38. Huybrechts KF, Palmsten K, Mogun H, *et al*. National trends in antidepressant medication treatment among publicly insured pregnant women. *Gen Hosp Psychiatry*. 2013; **35**(3): 265–271.
39. Le Strat Y, Dubertret C, Le Foll B. Prevalence and correlates of major depressive episode in pregnant and postpartum women in the United States. *J Affect Disord*. 2011; **135**(1–3): 128–138.
40. Lee AM, Lam SK, Sze Mun Lau SM, Chong CS, Chui HW, Fong DY. Prevalence, course, and risk factors for antenatal anxiety and depression. *Obstet Gynecol*. 2007; **110**(5): 1102–1112.
41. Coelho HF, Murray L, Royal-Lawson M, Cooper PJ. Antenatal anxiety disorder as a predictor of postnatal depression: a longitudinal study. *J Affect Disord*. 2011; **129**(1–3): 348–353.
42. Cohen LS, Altshuler LL, Harlow BL, *et al*. Relapse of major depression during pregnancy in women who maintain or discontinue antidepressant treatment. *JAMA*. 2006; **295**(5): 499–507.
43. MacQueen GM, Frey BN, Ismail Z, *et al*. Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 clinical guidelines for the management of adults with major depressive disorder: section 6. special populations: youth, women, and the elderly. *Can J Psychiatry*. 2016; **61**(9): 588–603.

44. Sockol LE. A systematic review of the efficacy of cognitive behavioral therapy for treating and preventing perinatal depression. *J Affect Disord*. 2015; **177**: 7–21.
45. Claridge AM. Efficacy of systemically oriented psychotherapies in the treatment of perinatal depression: a meta-analysis. *Arch Womens Ment Health*. 2014; **17**(1): 3–15.
46. Dennis CL, Allen K. Interventions (other than pharmacological, psychosocial or psychological) for treating antenatal depression. *Cochrane Database Syst Rev*. 2008;(4): cd006795.
47. Ross LE, Grigoriadis S. Selected pregnancy and delivery outcomes after exposure to antidepressant medication. *JAMA Psychiatry*. 2014; **71**(6): 716–717.
48. Ornoy A, Koren G. Selective serotonin reuptake inhibitors during pregnancy: do we have now more definite answers related to prenatal exposure? *Birth Defects Res*. 2017; **109**(12): 898–908.
49. Oberlander TF, Bateman BT, Palmsten K, *et al*. Neonatal outcomes after prenatal exposure to selective serotonin reuptake inhibitor antidepressants and maternal depression using population-based linked health data. *Arch Gen Psychiatry*. 2006; **63**(8): 898–906.
50. Malm H, Sourander A, Gissler M, *et al*. Pregnancy complications following prenatal exposure to SSRIs or maternal psychiatric disorders: results from population-based national register data. *Am J Psychiatry*. 2015; **172**(12): 1224–1232.
51. Huybrechts KF, Bateman BT, Palmsten K, *et al*. Antidepressant use late in pregnancy and risk of persistent pulmonary hypertension of the newborn. *JAMA*. 2015; **313**(21): 2142–2151.
52. Liu X, Agerbo E, Ingstrup GK, *et al*. Antidepressant use during pregnancy and psychiatric disorders in offspring: Danish nationwide register based cohort study. *BMJ*. 2017; **358**: j3668.
53. Bellantuono C, Vargas M, Mandarelli G, *et al*. The safety of serotonin-noradrenaline reuptake inhibitors (SNRIs) in pregnancy and breastfeeding: a comprehensive review. *Hum Psychopharmacol*. 2015; **30**(3): 143–151.
54. Smit M, Dolman KM, Honig A. Mirtazapine in pregnancy and lactation—a systematic review. *Eur Neuropsychopharmacol*. 2016; **26**(1): 126–135.
55. Cole JA, Modell JG, Haight BR, *et al*. Bupropion in pregnancy and the prevalence of congenital malformations. *Pharmacoepidemiol Drug Saf*. 2007; **16**(5): 474–484.
56. Newport DJ, Hostetter AL, Juul SH, *et al*. Prenatal psychostimulant and antidepressant exposure and risk of hypertensive disorders of pregnancy. *J Clin Psychiatry*. 2016; **77**(11): 1538–1545.
57. Alwan S, Reefhuis J, Botto LD, *et al*. Maternal use of bupropion and risk for congenital heart defects. *Am J Obstet Gynecol*. 2010; **203**(1): 52e1–6.
58. Huybrechts KF, Hernandez-Diaz S, Avorn J. Antidepressant use in pregnancy and the risk of cardiac defects. *N Engl J Med*. 2014; **371**(12): 1168–1169.
59. Briggs G. Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risk. In: R. Freeman, ed, *Sertraline*. Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins Health; 2015; 1254–1259.
60. Hendrick V, Stowe ZN, Altshuler LL, *et al*. Placental passage of antidepressant medications. *Am J Psychiatry*. 2003; **160**(5): 993–996.
61. Pinheiro E, Bogen DL, Hoxha D. Sertraline and breastfeeding: review and meta-analysis. *Arch Womens Ment Health*. 2015; **18**: 139–146.
62. Vasilakis-Scaramozza C, Aschengrau A, Cabral J, Jick SS. Antidepressant use during early pregnancy and the risk of congenital anomalies. *Pharmacotherapy*. 2013; **33**(7): 693–700.
63. Robakis TK, Williams KE. Biologically based treatment approaches to the patient with resistant perinatal depression. *Arch Womens Ment Health*. 2013; **16**(5): 343–351.
64. Sharma V, Khan M, Corpse C, Sharma P. Missed bipolarity and psychiatric comorbidity in women with postpartum depression. *Bipolar Disord*. 2008; **10**(6): 742–747.
65. Pugh NE, Hadjistavropoulus HD, Hampton AJ, *et al*. Client experiences of guided internet cognitive behavior therapy for postpartum depression: a qualitative study. *Arch Womens Ment Health*. 2015; **18**(2): 209–219.
66. O'Mahen HA, Richards DA, Woodford J, *et al*. Netmums: a phase II randomized controlled trial of a guided Internet behavioural activation treatment for postpartum depression. *Psychol Med*. 2014; **44**(8): 1675–1689.
67. Wozney L, Olthuis J, Lingley-Pottie P, *et al*. Strongest Families™ Managing Our Mood (MOM): a randomized controlled trial of a distance intervention for women with postpartum depression. *Arch Womens Ment Health*. 2017; **20**(4): 525–537.
68. Ngai FW, Wong PW, Leung KY, *et al*. The effect of telephone based cognitive-behavioral therapy on postnatal depression: a randomized controlled trial. *Psychother Psychosom*. 2015; **84**(5): 294–303.
69. Misri S, Reebye P, Corral M, *et al*. The use of paroxetine and cognitive-behavioral therapy in postpartum depression and anxiety: a randomized controlled trial. *J Clin Psychiatry*. 2004; **65**(9): 1236–1241.
70. Appleby L, Warner R, Whitton A, *et al*. A controlled study of fluoxetine and cognitive-behavioral counseling in the treatment of postnatal depression. *BMJ*. 1997; **314**(7085): 932–936.
71. Bloch M, Meiboom H, Lorberblatt M, *et al*. The effect of sertraline add-on to brief dynamic psychotherapy for the treatment of postpartum depression: a randomized, double-blind, placebo-controlled study. *J Clin Psychiatry*. 2012; **73**(2): 235–241.
72. Cuijpers P, De Wit L, Weitz E, *et al*. The combination of psychotherapy and pharmacotherapy in the treatment of adult depression: a comprehensive meta-analysis. *Journal of Evidence-Based Psychotherapies*. 2015: 147–168.
73. Thomson M, Sharma V. Therapeutics of postpartum depression. *Expert Rev Neurother*. 2017; **17**(5): 495–507.
74. Eberhard-Gran M, Eskild A, Opjordsmoen S. Use of psychotropic medications in treating mood disorders during lactation: practical recommendations. *CNS Drugs*. 2006; **20**(3): 187–198.
75. Kendall-Tackett K, Hale TW. The use of antidepressants in pregnant and breastfeeding women: a review of recent studies. *J Hum Lact*. 2010; **26**(2): 187–195.
76. Sharma V, Sommerdyk C. Are antidepressants effective in the treatment of postpartum depression? A systematic review. *Prim Care Companion CNS Disord*. 2013; **15**(6): PCC.13r01529.
77. De Crescenzo F, Perelli F, Armando M, *et al*. Selective serotonin reuptake inhibitors (SSRIs) for post-partum depression (PPD): a systematic review of randomized clinical trials. *J Affect Disord*. 2014; **152–154**: 39–44.
78. Hantsoo L, Ward-O'Brien D, Czarkowski KA, *et al*. A randomized, placebo-controlled, double-blind trial of sertraline for postpartum depression. *Psychopharmacology (Berl)*. 2014; **231**(5): 939–948.
79. Wisner KL, Perel JM, Peindl KS, *et al*. Prevention of postpartum depression: a pilot randomized clinical trial. *Am J Psychiatry*. 2004; **161**(7): 1290–1292.
80. Chaudron LH, Schoenecker CJ. Bupropion and breastfeeding: a case of a possible infant seizure. *J Clin Psychiatry*. 2004; **65**(6): 881–882.
81. Sharma V, Khan M. Identification of bipolar disorder in women with postpartum depression. *Bipolar Disord*. 2010; **12**(3): 335–340.
82. Sharma V, Sommerdyk C, Xie B. Aripiprazole augmentation of antidepressants for postpartum depression: a preliminary report. *Arch Womens Ment Health*. 2015; **18**(1): 131–134.
83. Freeman MP, Smith KW, Freeman SA, *et al*. The impact of reproductive events on the course of bipolar disorder in women. *J Clin Psychiatry*. 2002; **63**(4): 284–287.

84. Marengo E, Martino DJ, Igoa A, *et al*. Unplanned pregnancies and reproductive health among women with bipolar disorder. *J Affect Disord*. 2015; **178**: 201–205.
85. Wisner KL, Hanusa BH, Peindl KS, Perel JM. Prevention of postpartum episodes in women with bipolar disorder. *Biol Psychiatry*. 2004; **56**(8): 592–596.
86. Meador KJ, Bkaer GA, Browning N, *et al*. Fetal antiepileptic drug exposure and cognitive outcomes at age 6 years (NEAD study): a prospective observational study. *Lancet Neurol*. 2013; **12**(3): 244–252.
87. Newport DJ, Stowe ZN, Viguera AC, *et al*. Lamotrigine in bipolar disorder: efficacy during pregnancy. *Bipolar Disord*. 2008; **10**(3): 432–436.
88. Chisolm MS, Payne JL. Management of psychotropic drugs during pregnancy. *BMJ*. 2016; **532**: h5918.
89. Ennis ZN, Damkier P. Pregnancy exposure to olanzapine, quetiapine, risperidone, aripiprazole and risk of congenital malformations. a systematic review. *Basic Clin Pharmacol Toxicol*. 2015; **116**(4): 315–320.
90. Rosso G, Albert U, Di Salvo G, *et al*. Lithium prophylaxis during pregnancy and the postpartum period in women with lithium responsive bipolar I disorder. *Arch Womens Ment Health*. 2016; **19**: 429–432.
91. Nora JJ, Nora AH, Toews WH. Letter: Lithium, Ebstein's anomaly, and other congenital heart defects. *Lancet*. 1974; **2**(7880): 594–595.
92. Patorno E, Huybrechts KF, Hernandez-Diaz S. Lithium use in pregnancy and the risk of cardiac malformations. *N Engl J Med*. 2017; **377**(9): 893–894.
93. Uguz F, Sharma V. Mood stabilizers during breastfeeding: a systematic review of the recent literature. *Bipolar Disord*. 2016; **18**(4): 325–333.
94. Diav-Citrin O, Shechtman S, Ornoy S, *et al*. Safety of haloperidol and penfluridol in pregnancy: a multicenter, prospective, controlled study. *J Clin Psychiatry*. 2005; **66**(3): 317–322.
95. Coughlin CG, Blackwell KA, Bartley C, *et al*. Obstetric and neonatal outcomes after antipsychotic medication exposure in pregnancy. *Obstet Gynecol*. 2015; **125**(5): 1224–1235.
96. Doyle K, Heron J, Berrisford G, *et al*. The management of bipolar disorder in the perinatal period and risk factors for postpartum relapse. *Eur Psychiatry*. 2012; **27**(8): 563–569.
97. Bergink V, Kushner SA. Lithium during pregnancy. *Am J Psychiatry*. 2014; **171**(7): 712–715.
98. Sharma V, Smith A, Maxmanian D. Olanzapine in the prevention of postpartum psychosis and mood episodes in bipolar disorder. *Bipolar Disord*. 2006; **8**(4): 400–404.
99. Sharma V, Khan M, Sommerdyk C. Quetiapine in the acute treatment of bipolar postpartum depression: a chart review. *J Clin Psychopharmacol*. 2015; **35**(6): 733–735.
100. Uguz F. Second-generation antipsychotics during the lactation period: a comparative systematic review on infant safety. *J Clin Psychopharmacol*. 2016; **36**(3): 244–252.
101. Sharma V, Mazmanian D. Sleep loss and postpartum psychosis. *Bipolar Disord*. 2003; **5**(2): 98–105.
102. Mirhosseini H, Moosavipoor SA, Nazari MA, *et al*. Cognitive behavioral development in children following maternal postpartum depression: a review article. *Electron Physician*. 2015; **7**(8): 1673–1679.
103. Angst J, Azorin JM, Bowden CL, *et al*. Prevalence and characteristics of undiagnosed bipolar disorder in patients with a major depressive episode: the BRIDGE study. *Arch Gen Psychiatry*. 2011; **68**(8): 791–798.
104. Sharma V, Corpse C. Is your depressed postpartum patient bipolar? *Curr Psychiatry*. 2011; **10**(6): 81–82.
105. Leonpacher AK, Liebers D, Pirooznia M, *et al*. Distinguishing bipolar from unipolar depression: the importance of clinical symptoms and illness features. *Psychol Med*. 2015; **45**(11): 2437–2446.
106. Dudek D, Jaeschke R, Siwek M, Maczka G, *et al*. Postpartum depression: identifying associations with bipolarity and personality traits. Preliminary results from a cross-sectional study in Poland. *Psychiatry Res*. 2014; **215**(1): 69–74.

Optional Posttest and CME Certificate

CME Credit Expires: November 30, 2020

Posttest Study Guide

NOTE: The posttest can only be submitted online. *The below posttest questions have been provided solely as a study tool to prepare for your online submission.* ***Faxed/mailed copies of the posttest cannot be processed*** *and will be returned to the sender. If you do not have access to a computer, contact NEI customer service at 888-535-5600.*

1. Janet is a 22-year old patient with major depressive disorder who is pregnant with her first child. She is deeply concerned about the effects of psychotropic agents on her developing baby. Which non-pharmacological treatment(s) have the best evidence for efficacy in the treatment of antenatal major depressive disorder?
   A. Cognitive behavioral therapy
   B. Interpersonal behavioral therapy
   C. Bright light therapy
   D. A and B
   E. All of the above

2. Susanna is a 28-year-old woman who gave birth to her second child approximately 3 weeks ago. Screening for postpartum depression reveals a score of 14 on the Edinburgh Postnatal Depression Scale (EPDS). An EPDS score of 14 indicates that this patient has:
   A. Possible depression
   B. Probable depression
   C. Severe depression

3. Patricia is a 31-year-old patient with major depressive disorder who is currently 2 months pregnant. She has been taking an antidepressant for the past 2 years with good response and would like to continue her current treatment regimen for the duration of her pregnancy. However, the patient expresses concerns over continuing antidepressant treatment during the postpartum period because she is planning to breastfeed. Which of the following statements is true regarding antidepressants and breastfeeding?
   A. Breastfeeding exposure to most antidepressants is 10-fold higher than in utero exposure
   B. First generation MAOIs should not be used during breastfeeding
   C. Among selective serotonin reuptake inhibitors (SSRIs), fluoxetine has the lowest relative infant dose

4. Andrea is a 27-year-old patient with bipolar disorder I whose symptoms have been successfully managed for the past 5 years with lamotrigine. Andrea and her husband are now planning to start a family and are considering stopping lamotrigine when Andrea gets pregnant. What is the relapse rate for women with bipolar disorder I or II who discontinue prophylactic mood stabilizer treatment during pregnancy?
   A. 23%
   B. 37%
   C. 65%

Optional Online Posttest and CME Certificate Instructions

There is no posttest fee nor fee for CME credits.

1. Read the article.
2. Complete the posttest and evaluation, available only online at www.neiglobal.com/CME (under "CNS Spectrums").
3. Print your certificate (passing score = 70% or higher).

Questions? call 888-535-5600, or email CustomerService@neiglobal.com