

Optimizing Mental Health for Women: Recognizing and Treating Mood Disorders Throughout the Lifespan

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CME Background

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This ACADEMIC HIGHLIGHTS section of *The Journal of Clinical Psychiatry* presents the highlights of the teleconference series “Best Practices for Management of Mental Health in Women: Focusing on Mood Disorders Throughout the Lifespan,” which was held on May 16, 2023. This report was prepared and independently developed by the CME Institute of Physicians Postgraduate Press, Inc., and was supported by an educational grant from Mylan Inc., a Viatrix Company.

The teleconference was co-chaired by Kathryn M. Abel, MA, MBBS, FRCP, FRCPSych, PhD, University of Manchester, Manchester, England, and Marlene P. Freeman, MD, Harvard Medical School, Boston, Massachusetts.

CME Objectives

After studying this article, you should be able to:

- Appraise the influence of the reproductive stage on mood disorders and comorbid psychiatric conditions in women
- Assess factors involved in the diagnoses of mood disorders in women and the differential diagnoses and common comorbidities
- Summarize evidence-based approaches for diagnosing and treating mood disorders in women

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None of the other planners, reviewers, and CME Institute staff for this educational activity have relevant financial relationships with ineligible companies to disclose.

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It is estimated that 8.4% of American adults, or 21 million,¹ had at least 1 major depressive episode in 2022, with 10.5% of women experiencing a major depressive episode compared to 6.2% of men.¹ Many women experience mood symptoms throughout their reproductive years and during menopausal transitions. Mood symptoms are well-recognized to be influenced by hormonal changes across a woman’s life during the menstrual cycle, pregnancy, postpartum, and perimenopause and menopause.^{2,3} The heterogeneity in the presentation of depressive disorders and the difficulty of differentiating between diagnoses and comorbidities are likely to contribute to delayed diagnoses and treatment. The potential impact of the reproductive stage and the associated hormonal fluctuations are crucial factors to be considered during a female patient’s evaluation. During the consultation, it is important to ascertain the woman’s perspective, which provides valuable insights into her life experiences and potential risk and resilience factors for psychiatric conditions. Involving patients in designing their own treatment strategies can help to develop more personalized approaches to treatment and care pathways, and collaboration between clinician, patient, and family is critical for optimal outcomes. The following Academic Highlights article presents an overview of a recent webinar in which the faculty present 3 cases representative of mood disorders that occur at different points across a woman’s reproductive life and discuss best practices in managing these presentations.

PREMENSTRUAL DYSPHORIC DISORDER

Premenstrual dysphoric disorder (PMDD) is an onset of serious mood symptoms during the luteal or premenstrual phase of a woman’s cycle, with symptoms diminishing within a few days of menstruation but recurring in most cycles over a year. Usually symptoms occur in the week prior to onset of menses, but for some women symptoms last throughout the luteal phase.^{4,5} The disorder causes significant impairment in a woman’s life, with interference in her day-to-day function. Symptoms vary but commonly include mood lability, tearfulness, irritability, low mood, anxiety, difficulty concentrating, lack of energy, sleep problems, feeling overwhelmed, or physical symptoms, among others.^{4,6}

Premenstrual symptoms typically begin during a woman’s 20s, although they may start earlier, and

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Faculty Financial Disclosure

Prof Abel has received consulting fees from Flo Health; has served on the advisory board for Karolinska Institute (ended); has received royalties from Cambridge and from Oxford University Presses and The Royal College of Psychiatrists Press; she is a stock shareholder in Google and Amgen. She is the UK's National Institutes for Health and Care Research National Lead for Mental Health; she has numerous research grant awards from UK's Research and Innovation partners and a Fellowship from the European Research Council.

Dr Freeman, as an employee of Massachusetts General Hospital, working with the MGH Clinical Trials Network and Institute, has had research funding from multiple pharmaceutical companies and NIMH. MGH National Pregnancy Registry has been sponsored by Alkermes, Inc. (2016-Present), Eisai, Inc. (2022-Present), Johnson & Johnson/Janssen Pharmaceuticals, Inc (2019-Present), Otsuka America Pharmaceutical, Inc. (2008-Present), Sage Therapeutics (2019-Present), Sunovion Pharmaceuticals, Inc. (2011-Present), Supernus Pharmaceuticals (2021-Present), and Teva Pharmaceutical Industries Ltd. (2018-Present). Past Sponsors include Forest/Actavis/Allergan (2016-2018), AstraZeneca Pharmaceuticals (2009-2014), AuroMedics Pharma LLC (2021-2022), Aurobindo Pharma (2020-2022), Ortho-McNeil-Janssen Pharmaceuticals, Inc (2009-2014), and Pfizer, Inc. (2009-2011). She has received advisory boards or consulting fees from Data Safety Committees and Independent Data Safety and Monitoring Committees from Janssen (Johnson & Johnson), Novartis, Neurocrine, Eliem, Sage, Brainify, Everly Health, Tibi Health, Relmada, Beckley Psytech, and Bria Biotech; received honoraria for speaking/teaching from WebMD, Medscape, Pri-Med, Postpartum Support International; and has received royalties from The Massachusetts General Hospital Female Reproductive Lifecycle and Hormones Questionnaire.

Review Process

The faculty members agreed to provide a balanced and evidence-based presentation and discussed the topics and CME objectives during the planning sessions. The faculty's submitted content was validated by CME Institute staff, and the activity was evaluated for accuracy, use of evidence, and fair balance by the Chair and a peer reviewer who is without conflict of interest.

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are often more prominent during her 30s through perimenopause.² Moderate to severe premenstrual symptoms are experienced by 8.6% of women aged 25–34, 11.2% of women aged 35–44, and 10.8% of women aged 45–54,⁷ but there may be significant ethnic and cultural effects on PMDD prevalence.⁸ It is important to differentiate PMDD from premenstrual syndrome, premenstrual exacerbation (PME) of other mood disorders, and other psychiatric disorders so that women can get the help they need and lead full lives (Figure 1).

Dr Freeman, professor of psychiatry at Harvard Medical School and the associate director of the Center for Women's Mental Health in the Department of Psychiatry at Massachusetts General Hospital, began the discussion by presenting the case of Ms A.

Case Presentation 1: Ms A

Ms A, a 35-year-old divorced mother of 2, reports notable mood worsening in the luteal phase of her menstrual cycle, noticing irritability, crying, and low mood. She has also noted that the symptoms have worsened as she has aged, with the symptoms starting in her early 20s. Ms A's symptoms have increasingly interfered with her relationships and her ability to function at work. She has a history of generalized anxiety disorder and was previously treated with 10 mg/d of escitalopram.

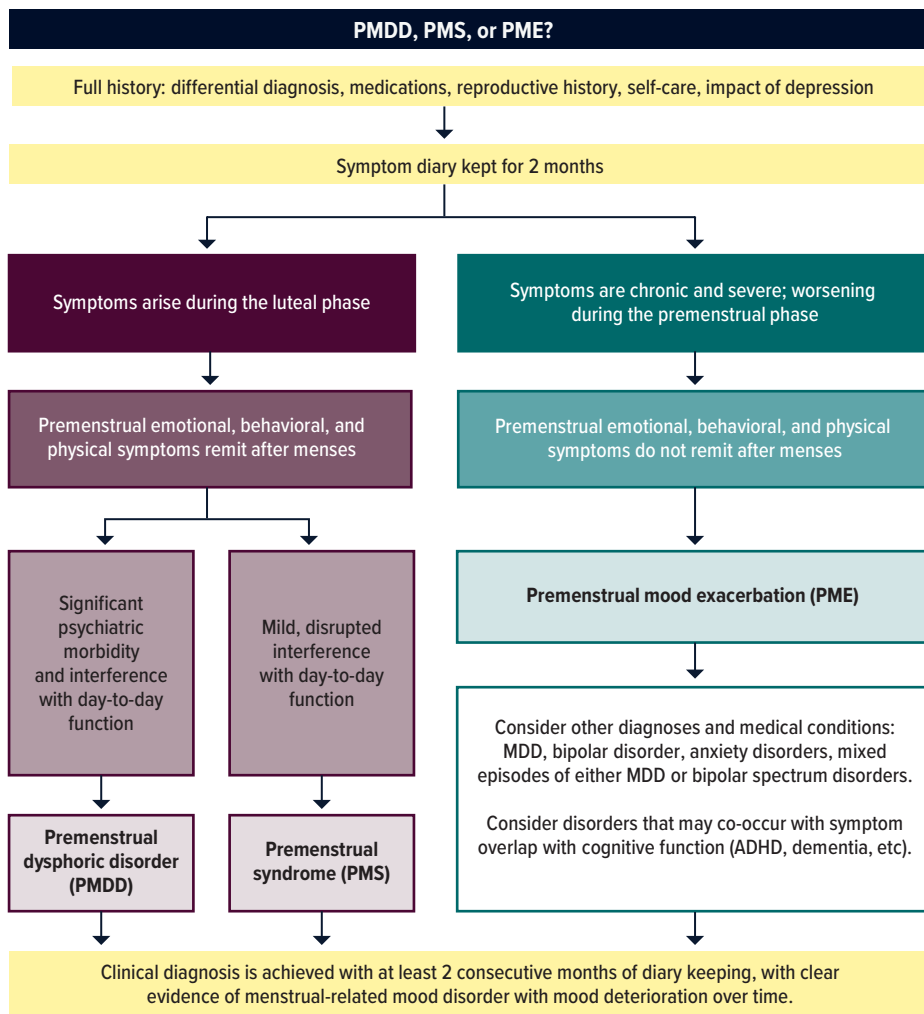
Diagnosis

To differentiate between PMDD and other possible diagnoses, clinicians should first take a full psychiatric, medical, and reproductive history, including menstrual cycle patterns and any known associated mood worsening, as well as other factors, such as contraception, pregnancy and postpartum experiences, quality of her relationships, and history of any traumatic experiences.⁹ "All of those may well influence the presentation of a deterioration in mood," Dr Abel, Professor of Psychological Medicine and Director of the Centre for Women's Mental Health at the University of Manchester, said. Accurate diagnosis of PMDD requires prospective tracking of the menstrual cycle and associated symptoms by diary keeping of at least 2 consecutive cycles. Precision in diagnosis is critical to ensure women are offered the most appropriate treatments.

Many women present with a co-occurring major depressive episode or an anxiety disorder for which they are already receiving treatment, but they may, nevertheless, need more targeted strategies to address premenstrual symptoms.^{10,11} If, in fact, they are experiencing worsening symptoms of another disorder during the luteal phase, such as bipolar disorder, this is usually referred to as PME rather than PMDD.¹² Dr Freeman pointed out the complication of patients' use of intrauterine devices or continuous dosing of oral contraceptive pills (OCPs), which masks or interferes with the regularity of the menstrual cycle and makes tracking more difficult.

Dr Abel added that some data suggest differences in the presentation of premenstrual symptoms and PMDD in ethnic minorities and among different socioeconomic groups, suggesting that more research is needed to guide personalized care.⁸

Figure 1.
Diagnosing PMDD, PMS, or PME



Abbreviations: ADHD = attention-deficit/hyperactivity disorder, MDD = major depressive disorder.

Treatment

The availability of multiple treatment options creates an opportunity for patients to become involved in their own treatment program, monitoring outcomes and working with their clinicians to optimize their care. Truly collaborative approaches to care require time and an appreciation of each woman’s circumstances eg, childcare responsibilities, work schedules, and what her most distressing symptoms are. These factors will be important in guiding her through the care pathway best suited to her needs.¹³

If symptoms are severe, medical treatments are considered first-line for PMDD and include serotonergic antidepressants and OCPs. The antidepressants with the most demonstrated efficacy include the selective serotonin reuptake inhibitors (SSRIs), such as sertraline, citalopram, escitalopram, or fluoxetine.¹⁴ If the patient is currently taking an SSRI, increasing their dosage, sometimes even transiently during the luteal phase,

may alleviate symptoms.¹⁴ Serotonin-norepinephrine reuptake inhibitors (SNRIs), such as venlafaxine, have also shown efficacy and may be a reasonable option, especially if the patient tolerates them better or does not respond to an SSRI.¹⁵ Guidelines suggest switching to another antidepressant after at least 2 menstrual cycles of treatment at an adequate dose.¹⁵ Antidepressants can be used either continuously or intermittently during the luteal phase to treat PMDD. If the patient is being treated with an antidepressant and is still suffering, it is reasonable to add an oral contraceptive to the regimen.¹⁵

OCPs are also considered a first-line treatment for PMDD and may be used with a placebo week during which patients have menstrual periods, or with continuous dosing, during which placebo weeks are skipped and therefore menstrual periods do not occur monthly. OCPs and antidepressants are often used together, and treatment can be individually tailored

to the preferences and symptoms of the patient.¹² OCPs are contraindicated in women above the age of 35 who smoke cigarettes; risks may outweigh benefits in women who have had problems with hypercholesterolemia, blood clotting disorders, strokes, and high blood pressure.¹⁶

As with any treatment-refractory condition, if patients do not respond, the diagnosis should be carefully reassessed. It is not uncommon to miss a diagnosis of bipolar disorder or major depressive disorder (MDD) unless symptoms are carefully tracked and assessed. In rare occasions when the patient is experiencing severe PMDD without relief from antidepressants, OCPs, and lifestyle modifications such as exercise and good nutrition, the clinician and patient team might work with reproductive endocrinologists and discuss using gonadotropin releasing hormone (GnRH) agonists or analogs, which shut down the ovarian hormone function, especially before considering a surgical and irreversible intervention such as a hysterectomy.¹⁶ If PMDD co-occurs with substantial menstrual pain, clinicians should assess for thyroid disorders and endometriosis.¹⁷

If a woman wishes to become pregnant, she should be advised that her symptoms are likely to reduce or disappear during pregnancy, and SSRIs should, therefore, be discontinued prior to and during pregnancy, unless use is justified by the cotreatment of another disorder, such as MDD or an anxiety disorder. Advice on how to safely stop treatment should be provided to all women taking SSRIs: women taking luteal phase SSRIs may be more able to discontinue the treatment safely at any time, whereas women using a continuous regimen should taper the dose more gradually over at least 2 months.

MAJOR DEPRESSIVE DISORDER

Major depressive episodes are defined as 2 or more weeks of feeling down or depressed and losing interest or pleasure in activities and can include sleep dysfunction, changes in appetite, trouble concentrating, low energy, and/or suicidal thoughts. Episodes may be a single episode or recurrent, chronic, or treatment resistant.¹⁸

Dr Freeman introduced the second case in the webinar with Ms B.

Case Presentation 2: Ms B

Ms B is a 23-year-old woman living with her male partner and presenting with low mood over several months, difficulty with motivation and activities of daily living, trouble sleeping, weight loss, and decreased interest and pleasure in activities. She does not report any suicidal ideation or a history of suicide attempts. She has had 3 previous episodes of major depression, 1 untreated and 2 treated with psychotherapy and SSRI antidepressants. She eventually wants to have children but is not presently planning to start a family.

Diagnosis

Taking the patient's history, including reproductive history, such as previous pregnancies, premenstrual mood worsening, and whether she has regular menstrual cycles, aids in understanding her course of illness and possible risk factors for future episodes of depression. Clinicians should also assess the patient's history to consider the differential diagnoses and possible co-occurring disorders, including bipolar disorder, anxiety disorders, posttraumatic stress disorder (PTSD) or trauma-related disorders, eating disorders, and substance misuse.¹⁹ "I always go back to early childhood," Dr Freeman said. "Psychiatric disorders often start early, and many women arrive at the reproductive years already having had a diagnosis of a psychiatric condition or having had the onset of one, even if they have not had treatment before."²⁰ For many, these are either chronic or recurrent conditions." Screening for past episodes of mania or hypomania and suicide attempts and trauma are critical in understanding aspects of the patient's history that may influence treatment selection and outcomes.

Along with assessing the patient's history, discussing methods of contraception for women who do not wish to become pregnant is key, as many pregnancies are unplanned (approximately 50% in the US), with 75% of teenage pregnancies unplanned.^{21,22} The UK additionally offers antenatal screening programs for mood disorders and includes questions to women about domestic violence. Domestic violence has become recognized as an important risk factor in women's lives, increasing the risk of mood disorders overall. Pregnancy has been identified as a time of particular risk for domestic violence.²³

Diagnosis during the postpartum period. Postpartum blues, postpartum depression (PPD), and postpartum anxiety each require their own treatment considerations, and clinicians need to know their specific symptoms and presentation. Postpartum blues is a normal, extremely common condition, characterized by a transient unexplained lability of mood with characteristic bouts of sadness or tearfulness, not to be confused with MDD, which impairs functioning and is pervasive.²⁴

PPD is the most common psychological disorder associated with childbirth: between 10%–15% of mothers experience postpartum major depressive episodes and symptoms such as difficulty sleeping, anxiety, and suicidal thoughts or plans.²⁵ The *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition, explains that a postpartum major depressive episode has an onset either in late pregnancy or within the first 4 weeks after delivery.²⁵ Women with a prior history of mental illness are also more likely to experience a range of obstetric complications,²⁵ and the most likely time a woman will develop a new-onset mood disorder or psychiatric episode across her life is within the first 3 weeks postpartum.^{26,27} The postpartum period is also a vulnerable time for new onset of bipolar disorder; however, women with

a prior history of bipolar disorder are at particularly high risk of postpartum mood disorders, making close monitoring and attention to sleep paramount.²⁸

Postpartum anxiety disorder can include obsessive compulsive symptoms or definitive obsessive-compulsive disorder (OCD), in which women experience recurrent, intrusive, distressing thoughts, often about the baby's health or harming her baby. Here, it is important for health care providers to differentiate OCD from postpartum psychosis.²⁹ Postpartum psychosis is a rare disorder but is considered a psychiatric emergency with a high relative risk of suicide requiring urgent care. It includes often quite bizarre psychotic symptoms, including delusions and/or hallucinations that may be related to the infant, and is usually accompanied by manic symptoms or cognitive changes.³⁰

In the UK, up to 5% of women present with PTSD after childbirth, particularly following traumatic peripartum events or obstetric complications. PTSD is often missed postpartum and is amenable to specific trauma-informed treatment paradigms.^{31,32}

Treatment

For MDD and anxiety disorders, cognitive behavioral therapy (CBT) or antidepressants are the first line of treatment depending on the severity of symptoms.³³ Nonpharmacologic approaches include evidence-based psychotherapies such as CBT. The ability for women to access talking therapies may vary considerably, however. Lifestyle approaches can also significantly influence a woman's mental health and include information and support for her maintaining a healthy regular exercise regimen, good sleep hygiene, and support for sleep antenatally and postnatally. Educating partners and family members about a woman's support needs is often overlooked but can be a critical element in her ability to recover. Balanced nutrition and mindfulness-based treatments like meditation are also to be encouraged.³³

Treatment during pregnancy. SSRIs are the most common antidepressants used during pregnancy and one of the most studied classes. While many women feel stigmatized, guilty, or alone about needing treatment during pregnancy, treatment is often needed, and untreated mood and anxiety disorders during pregnancy are major predictors of severe postpartum psychiatric worsening. Importantly, SSRIs do not appear to be associated with the increased risk of birth defects.³³ Women with recurrent depressive episodes may need maintenance antidepressants to stay well during pregnancy, and those in the midst of a major depressive episode that is moderate to severe may require initiating an antidepressant or restarting one. Antidepressants are also considered the best studied class of medication during breastfeeding.³³

There is much confusion about whether antidepressants should be continued or discontinued

Clinical Points

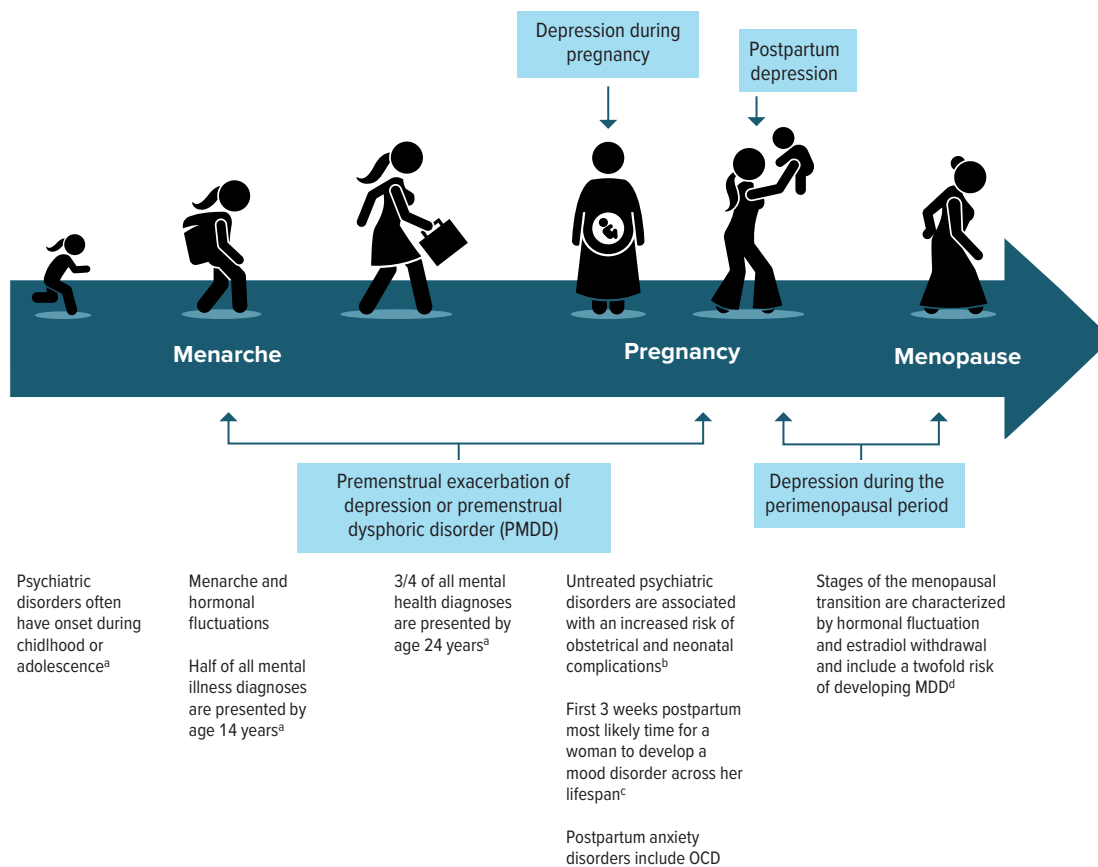
- Women are affected by depressive disorders across the reproductive lifespan and are likely to experience complex presentations and needs. Early and regular assessment of and treatment interventions for these diagnoses in female patients can have a significant impact on patients' lives and those of their families.
- Spending time with patients, taking a full history, and taking the time to understand each patient's perspective during each period of a woman's life lead to more accurate diagnoses, ultimately facilitating more effective treatment plans.
- Many options are available to treat the spectrum of mood disorders women may experience. Discussing options with them and involving them in their own care help women to make the best decisions for themselves and provide an opportunity for individualized, patient-centered, evidence-based care so that they can be in remission as much as possible and lead a full life.

during the third trimester, because in the past it has been suggested that they be discontinued to prevent neonatal symptoms that have been observed after in utero exposure to antidepressants. Consensus among perinatal psychiatrists reflects that it is not a good idea to discontinue antidepressants in the third trimester, because the postpartum is a time of increased risk of psychiatric worsening. Untreated psychiatric disorders are associated with an increased risk of obstetric and neonatal complications.³³ Many women think they are doing something better for their child by forgoing care; however, Drs Abel and Freeman emphasize that taking good care of themselves is taking good care of their babies.

In tandem with these types of treatments, clinicians should monitor the overall health of the mother, particularly with regard to maintaining a healthy diet and weight, which can affect pregnancy outcomes, as well as discussing the use of tobacco, alcohol, illicit drugs, and marijuana. "The landscape has really changed for marijuana," Dr Freeman said. "Everything we've learned about the use of marijuana during pregnancy is that it has only negative effects on pregnancy and child developmental outcomes."³⁴ It is also important to inquire about folic acid or multivitamin use. The addition of folic acid before a pregnancy or in early pregnancy can help prevent birth defects, is very important for neurodevelopment, and may also have a preventative role in some psychiatric disorders.³⁵ Women with severe mental illness are likely to have poorer reproductive health and obstetric outcomes and may be less likely to access folate, so particular care should be taken in monitoring their intake antenatally.³⁶

Treatment during the postpartum period. Coming back to the topic of postpartum psychosis, Dr Freeman

Figure 2.
Mood Disorders Throughout the Lifespan



^aData from Insel and Fenton.⁴¹ ^bData from Wichman and Stern.³³ ^cData from Chechko et al²⁶ and Munk-Olsen et al.²⁷ ^dData from Freeman et al.³⁶

Abbreviations: MDD= major depressive disorder, OCD= obsessive-compulsive disorder.

remarked that the US population lacks education on postpartum psychosis (PPP), often resulting in a delay of women seeking help. PPP almost always requires hospitalization, due to the risk of suicide or infanticide, and women with PPP should receive a full workup and initiate the proper treatment.³⁰ For PPD, brexanolone is a new neurosteroid that was approved by the US FDA for this indication, a first in recognizing PPD as an indication for a new medication approval.³⁷ More recently, the oral neurosteroid zuranolone has also received approval for PPD from the FDA.

Clinicians need to weigh the risks and benefits of any treatment for each individual so that they can tailor decisions and meet the goals of treatment, which are to help women live the lives that they want to be living. The FDA's recognition of PPD as an indication for treatment in the US has generated educational efforts around the disorder, as well as a growing interest in clinical research efforts to address it.

MENOPAUSE

The average age of menopause is approximately 50; however, hormonal fluctuations and the withdrawal of estrogen may start as early as 30.³⁸ Estrogen has been shown to have antidepressant effects, and experimentally induced estradiol withdrawal has been demonstrated to trigger mood symptoms in some women in a laboratory setting.³⁹ Women have at least a 2-fold increase in the risk of experiencing major depression around menopause.³⁶ Those with a history of a reproductive mood disorder such as PPD or PMDD have a 13% greater risk of experiencing a mood disorder around menopause than those without such a history, while those with a history of MDD at any time in their lives have a 12% greater risk.^{36,40} Awareness of these risks provides a window of opportunity to identify these disorders and possibly prevent them. See Figure 2 for a depiction of mood disorders throughout the female lifespan.

Professor Abel introduced the third case in the webinar with Ms C.

Case Presentation 3: Ms C

Ms C is a 54-year-old married woman with grown children. At 52 she began to notice hot flashes, decreased sleep, and sleep disturbance. Her menstrual cycle is more irregular, and more recently she has been experiencing moodiness, irritability and low mood, decreased enjoyment of activities in her life, feeling foggy in her brain, and finding she has been unable to concentrate. These symptoms are also interfering with her ability to work.

Differentiation

The 2 most common symptoms of menopause are chronic sleep problems and hot flashes, with a 2-fold increase in sleep disturbance in menopausal women⁴² and 60%–80% of women experiencing intense feelings of heat at night.⁴³ Menopause is also a risk factor for sleep apnea, as are age, being overweight, smoking, and drinking alcohol.⁴⁴

During the menopausal transition, it is important to determine whether the patient is experiencing a recurrent depressive episode or a new-onset mood disorder. Taking a history of prior mood disorder linked to a woman's reproductive life can help in this assessment. It is also important to assess for evidence of thyroid disease; hypothyroidism, in particular, is common and may have overlapping symptoms with MDD. Dr Abel reiterated that clinicians need to be aware of ethnic/racial differences in presentation of mood disorders, with vasomotor, mood, and sleep symptoms particularly more likely to present in African-American women.⁴⁵

Treatment

Talking to women about how their symptoms interfere with their lives is an important precursor to developing a care pathway. Treatment strategies for perimenopause and menopause should include lifestyle factors such as diet and exercise. In their 2018 guidelines, the North American Menopause Society and the Women and Mood Disorders Task Force of the National Network of Depression Centers defined SSRIs and psychotherapy as first-line treatments for perimenopausal depressive symptoms and MDD episodes.⁴⁶ Large studies have demonstrated the benefits of SSRIs and SNRIs for both hot flashes and sleep, and there are emerging data of their benefits for perimenopausal depression specifically.^{47,48}

In the UK the use of hormone replacement therapies (HRT) is encouraged as first-line treatment for vasomotor and other physical symptoms unless contraindicated (such as estrogen-sensitive cancer history or family history and/or history or risk of embolism). HRT has also been suggested to improve mood.⁴⁹ Although it is not approved

to treat perimenopausal depression in the US, evidence shows that estrogen therapy has antidepressant effects in perimenopausal women, particularly those with concomitant vasomotor symptoms.⁴⁶ In the US, it is recommended only for more severe menopausal symptoms and for as short a period as possible.⁵⁰ Typically, in the US, antidepressants are first line for MDD during the menopausal transition, with estrogen considered as augmentation. The transdermal patch of estrogen may be less risky in terms of blood clots and is used more commonly.⁵¹

There is also evidence that gabapentin can help hot flashes and sleep disturbance, and clinicians should consider the impact of insomnia and treat it with medications and non-pharmacologic interventions as appropriate.^{48,52,53} “We really want to focus on individualized, patient-centered, evidence-based approaches,” Dr Freeman said. “The female reproductive life span is complex.” Individualizing treatment requires educating patients about psychiatric disorders and the possible impact of reproductive events. This education can help them participate in making collaborative treatment decisions that are individualized to their needs.

Drs Freeman and Abel closed with providing several resources for patients, families, and clinicians, including Postpartum Support International, the National Maternal Mental Health Hotline, the Depression and Bipolar Support Alliance, and the National Alliance on Mental Illness. Non-US resources include Mind, the Royal College of Psychiatrists' information on postpartum psychosis, Tommy's (a pregnancy charity), National Institute for Health and Care Excellence guidance for clinicians, and the National Health Service website for patients.^{54–58}

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