Menopause and Mood

The Role of Estrogen in Midlife Depression and Beyond

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KEYWORDS

• Depression • Perimenopause • Menopause • Estrogen • Treatments

KEY POINTS

- Depression is a prevalent, disabling condition.
- Midlife women are more vulnerable to develop depression (new onset or recurrent), often associated with vasomotor symptoms and sleep problems.
- Therapies should be tailored to alleviate all these symptoms and improve quality of life, while taking into consideration pharmacologic, behavioral, and/or hormonal options.

INTRODUCTION

The impact of mental illnesses (including substance use disorders) on the overall health of individuals and the society at large can no longer be disregarded or minimized. Recent estimates indicate that at least 1 billion individuals worldwide are affected by mental illnesses, a staggering number that represents approximately 15% of the world's adult population.[1] Depression is the most prevalent, disabling condition among all mental illnesses. The World Health Organization estimates that 300 million people suffer from depression worldwide, resulting in significant costs for individuals, their families, and their communities.[2]

Throughout the course of the COVID-19 pandemic, we have witnessed a dramatic increase in the prevalence of mental illnesses across all ages, with particularly high rates of depression, anxiety, and substance use disorders among both men and women. Data suggest that such increase was multifactorial, likely linked to the disruption of social support systems that are integral components of mental health services, the consequences of prolonged social isolation, financial concerns, food insecurity, grief, and bereavement, among others.[3]

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The enduring, adverse effects of COVID-19 on mental health of women across the lifespan will be examined for years to come; it is unquestionable though that women's mental health has been affected during the pandemic, with systematic reviews already signaling higher rates of depression and anxiety in women compared with men.[4] For example, increased rates of anxiety and depression were documented among women who experienced pregnancies or a postpartum period during the COVID-19 pandemic, particularly when subjected to social restrictions and prolonged lockdowns.[5] Elderly women also experienced the impact of the pandemic on various aspects of their health and well-being, including limited access to care (ie, getting routine care or timely access to appointments), difficulties in renewing prescriptions, or having access to in-person caregivers.[6]

Overall, it has been long known that women are more affected by depression and anxiety than men, with a 1.5- to 2.0-fold increased risk (point prevalence) for either of these disorders. The burden and disability associated with these conditions have also grown disproportionally among women over the past few decades.[1] Clinicians and researchers have documented an increased risk for developing depression (new onset and/or recurrent) among some women at certain points in time across their reproductive life cycle. This observation has led to the conceptual framework of *reproductive-related windows of vulnerability* for depression. Essentially, hormonal changes could be contributing to the emergence of mood symptoms and/or influencing their clinical presentation and severity. This would be the case, for example, of women experiencing mood symptoms and dysphoria during the luteal phase of their menstrual cycles, the emergence of depressive symptoms during puerperium or depression associated with the menopausal transition.[7]

The worsening of other mental health conditions has been associated with periods of intense, sometimes chaotic hormonal changes across the female lifecycle. Premenstrual worsening of symptoms has been documented among women with diagnosis of anxiety disorders, psychotic disorders, depression, and borderline personality disorder[8,9]; suicidality can also increase premenstrually.[10]

During the midlife transition, women may experience the compounding effects of psychological stressors and physical changes, the latter including metabolic issues, cardiovascular diseases, diabetes, osteoporosis, osteoarthritis, chronic pain, and so forth. In addition, the emergence of menopause-related problems such as vasomotor symptoms (VMS) and sleep disruptions may ultimately affect a woman's quality of life and overall functioning.[11–13]

Menopause and Depression

Depressive symptoms are characterized by low mood, reduced motivation, poor engagement in usual activities, limited enjoyment, and disrupted sleep; depressive symptoms seem to increase during the menopause transition and are often associated with psychosocial impairment and poorer quality of life.[14–16] A high prevalence of depressive symptoms among midlife women has now been confirmed by cross-sectional and longitudinal studies, even among those who had never been diagnosed with depression before. Major depressive episodes (MDDs), although less common than depressive symptoms, are also more commonly observed during midlife years. Previous studies indicated a 2- to 4-fold increased risk for MDD during the menopause transition compared with the premenopausal or postmenopausal years. The occurrence of depression (rather than depressive symptoms) was documented in cohort studies that followed women throughout the menopause transition and early postmenopausal years, and the increased risk was particular high for recurrent depressive episodes, that is, among those with prior history of depression.[17,18]

One could examine the occurrence of depression (MDD or depressive symptoms) during midlife years through the lens of 2 clusters of factors: continuum-related factors and window-related factors. *Continuum-related* factors are those that are pervasive in nature and may "follow" a woman throughout her life journey—they include socioeconomic conditions, psychosocial stressors, and their overall health, just to name a few. The strongest predictor for the occurrence MDD during midlife years is, however, a previous diagnosis of MDD, which means depression is more likely to reoccur during midlife years, rather than emerging as a new condition, for the first time.

Window-related factors are, on the other hand, more time related or context related; they are usually understood as mediating or precipitating factors for the occurrence of MDD among midlife women. Among window-related factors we consider the occurrence of significant hormone variations and the emergence of menopause-related symptoms (sleep problems, vasomotor symptoms); the experience of stressful life events, particularly when those occur closely in time to the menopause transition; and the presence of chronic medical conditions that might worsen during midlife years.[19–24] Health care professionals should be able to recognize moderating (continuum-related) and mediating (window-related) factors in order to better prevent, detect, and/or effectively treat depression during midlife years and beyond.

The Effects of Estrogen on Mood

Estrogen (E) has neuromodulatory effects, primarily through its interactions with monoaminergic systems that involved in mood regulation, such as serotonin (5-hydroxytryptamine [5-HT]) and noradrenaline (NE). Such effects are, overall, deemed to be beneficial to mood.[25–27] The administration of estradiol (E2), for example, may result in a net increase in 5-HT synthesis; this increase occurs through various mechanisms, including the reduction of enzymes involved in 5-HT degradation and an increase in tryptophan hydroxylase, the enzyme that is necessary for serotonin synthesis. Estradiol also increases 5-HT availability by downregulating $5HT_{1a}$ autoreceptors and upregulating $5HT_{2a}$ receptors in the synaptic cleft, thus increasing 5-HT availability for postsynaptic transmission.[28,29]

Estrogen also increases NE synthesis through similar mechanisms to those described for serotonin and likely has neuroprotective effects by stimulating the release of brain-derived neurotrophic factor.[30,31]

Consistent with the aforementioned neuromodulatory effects of E2, there are now several studies that correlate intense fluctuations in E2 levels with the development of perimenopausal depression. There are at least 3 studies that documented a relationship between greater, wider fluctuations in E2 levels and an increased risk for developing depressive symptoms.[21,22] Schmidt and colleagues also demonstrated such association in an experiment in which they produced an E2 withdrawal after administering E2 (transdermal) to women with a history of perimenopausal depression that had been responsive to E2.[32]

The GABAergic deficit hypothesis for depression has gained increasing attention. The serotonergic and GABAergic systems are known to be interconnected; with that, it has been postulated that deficiencies in GABAergic neural inhibition could contribute to the occurrence depressive symptoms across a woman's reproductive life cycle; conversely, the restoration of the GABAergic neurotransmission could produce antidepressant effects—this seems to be one of the plausible mechanisms for the antidepressant effects exerted by estrogen and allopregnanolone (ALLO).[33]

There is now strong evidence suggesting a mediating effect of ALLO (ie, heightened sensitive to ALLO fluctuations) for the association between changes in reproductive steroid hormones and mood in the context of PMDD[34] and postpartum depression.[35]

However, it has yet to be determined the extent to which a similar sensitivity may play a role in the development of perimenopausal depression. In one study involving late perimenopausal and early postmenopausal women (n = 140), a negative correlation was found between serum ALLO levels and feelings of guilt among the early postmenopausal women, likely coinciding with a hypogonadal state.[36]

Estrogen-Based Therapy for Depression

Despite accumulated, preclinical evidence demonstrating the antidepressant properties of estrogen therapy (ET), its use in clinical practice has been limited. Two randomized controlled trials[37,38] demonstrated the efficacy and safety of transdermal estradiol for the treatment of MDD and led to the inclusion of E2 therapy into the 2016 Clinical Guidelines of the Canadian Network for Mood and Anxiety Treatments (CANMAT), as a second-line treatment (level 2) for the management of MDD during perimenopause.[39] Both studies used standardized procedures to confirm the diagnosis of depression and to properly characterize menopausal staging; antidepressant effects were significant—similar to those observed with conventional antidepressants—and mood improvements were documented among women with new or recurrent depression, with and without concomitant vasomotor symptoms. It is important to note that the use of similar intervention (transdermal E2) for depression in late *postmenopausal* women failed to show positive results,[40] reinforcing the notion that the menopause transition might be not only a critical window for the occurrence of depression but a *window of opportunity* for the antidepressant use of ET.[41] It is undeniable, however, that the knowledge dissemination regarding the promising antidepressant benefits of E2 therapy for midlife depression and the development of further clinical investigations in this field were for years curtailed by the negative views, lack of nuanced analyses, and misconceptions on estrogen therapies that were generated by the Women's Health Initiative study; some of these misconceptions have lasted for a decade, despite numerous efforts by clinicians and researchers to provide some context to the study analyses and their limitations.[42]

Estrogen has been studied as a prophylactic approach to prevent the development of depressive symptoms in midlife women.[43] The use of transdermal estradiol (100 μg) plus intermittent oral micronized progesterone for 12 months led to a reduction in the risk of developing depressive symptoms compared with the use of placebo (32.3% vs 17.3%, respectively), when administered to women in early perimenopause. Interestingly, prophylactic E2 effects were more pronounced among women who had experienced stressful life events in the preceding 6 months of the study.

Based on existing data and accumulated clinical experience, it is reasonable to consider E2 as part of the treatment armamentarium for midlife depression; clinicians should consider a brief trial with E2 (4–6 weeks), particularly for women in the menopause transition who present with depressive symptoms and concomitant VMS. The evidence is also supportive of the use of transdermal E2, rather than other formulations or routes of administration. The use of E2 should be considered as an option for symptomatic midlife women suffering from depression who are unable or unwilling to initiate treatment with antidepressants or other therapies.[24]

Menopause, Anxiety, and Estrogens

Despite being identified as a significant contributing factor to poorer quality of life and impaired functioning among midlife women, anxiety does not often receive the same attention of studies and clinical trials compared with that dedicated to depression. Longitudinal studies revealed an increase of anxiety and its various components (eg, irritability, nervousness or tension, fearfulness, and heart racing) across different

menopausal staging. In the SWAN study, women with high anxiety at baseline (ie, premenopausal) experienced a peak in anxiety during late perimenopausal years, with a subsequent decline in the postmenopausal period; anxiety was experienced by women even in the absence of other menopause-related symptoms, which reiterates the importance of proper screening and disease awareness among clinicians.[44]

For a significant number of midlife women, anxiety is strongly associated with the presence and severity of hot flashes. In the Penn Ovarian Aging Cohort, somatic anxiety (eg, chest pain, fatigue, dizziness) was found to be significantly associated with hot flashes in the menopause transition, even after adjusting for factors such as age, menopausal staging, reproductive hormone levels, history of depression, and others. Importantly, somatic anxiety *preceded* the occurrence of hot flashes.[45] A recent Japanese study also revealed independent associations between VMS and anxiety and distressing burden caused by rapid or irregular heartbeats (palpitations).[46]

The association between E2 fluctuations and symptoms of anxiety and anhedonia were examined in a recent study in which 73 women (aged 49 $\pm$ 3 years) were submitted to a social anxiety test (Trier social stress tests [TSST]) at study entry, at week 8 and week 16. Study participants were randomly assigned to receive 8 weeks of transdermal estradiol (0.1 mg per24 hours) or placebo. Hormone measurements were collected for 8 weeks before the treatment allocation (E2 or placebo) and throughout the experiment. Greater E2 fluctuations over the initial 8-week period (ie, before treatment allocation) predicted the presence of greater symptoms of anxiety and a higher cortisol reactivity to TSST. Moreover, transdermal E2 was effective in improving symptoms of anxiety and anhedonia. Therapy with E2 was particularly helpful for those who exhibited high baseline E2-anxiety sensitivity. If further confirmed, this intervention could be particularly beneficial for midlife women with somatic symptoms and for those who seem to be more vulnerable to develop anxiety in the context of E2 fluctuations.[47]

Managing Midlife Depression—a Treatment Framework

Antidepressants and behavioral interventions remain the first-line treatment of depression across the life span. The use of antidepressants should be prioritized for women who experienced multiple depressive episodes in the past (ie, not exclusively hormone related) and/or those reporting severe depressive symptoms, functional impairment, or suicidal ideation.

A frequently asked question by patients and health care providers is whether there could be a preferred option or choice of a particular agent for the management of depression in midlife women; to address this question, an important distinction needs to be made between new-onset and recurrent episodes. For recurrent episodes, a previous response to a specific antidepressant (agent, class) should influence the decision on what to try first—if a particular medication was helpful in the past, this should be considered. For those who are experiencing depression for the first time during midlife years, those who are treatment-naive, or those presenting with partial or no response to antidepressants in the past, there is evidence of the efficacy and safety of various agents—at usual doses compared with other stages in life. That includes the use of fluoxetine, sertraline, venlafaxine, citalopram, escitalopram, duloxetine, desvenlafaxine, and vortioxetine for depressed, menopausal women.[48–56] Overall, there no evidence to support a superior efficacy of a particular antidepressant agent or class over the others for the management of midlife depression. In a randomized, double-blind study of *postmenopausal* women (aged 40–70 years) with diagnosis of MDD, both desvenlafaxine (100–200 mg/d) and escitalopram (10–20 mg/d) led to significant and comparable results, either after an 8-week acute treatment or during a 6-

month continuation phase. These results did not support the hypothesis that serotonin and norepinephrine reuptake inhibitors (SNRIs) could have an efficacy advantage for the treatment of MDD in postmenopausal women.[55] The study, unfortunately, did not include more accurate information on time since menopause to better explore the hypothesis that the lack of superior efficacy of an SNRI over an selective serotonin reuptake inhibitor observed in this study could have been due to the timing of the antidepressant intervention—that is, depressive women in the menopausal transition and early postmenopausal years could have benefited more from SNRIs due to the occurrence of wide estrogen fluctuations during this period and the putative impact of these hormone changes on mood and behavior.

In one recent study, venlafaxine was found to be superior to fluoxetine for the treatment of MDD in postmenopausal women (average 57 years of age); the study, however, include a wide dose range for venlafaxine (75–225 mg/d) and fluoxetine (20–60 mg/d), which could have affected both norepinephrine effects of venlafaxine (when administered at lower doses) and the tolerability of fluoxetine (when used at higher doses).[57]

Information on tolerability should be part of the discussion for the selection of antidepressants for midlife women, particularly when sexual dysfunction and changes in weight are of concern. Existing data on the efficacy of some agents for menopause-related symptoms (VMS, pain, disrupted sleep) and quality-of-life improvement could also help guide clinicians. Drug-drug interactions need to be considered, given that perimenopausal and postmenopausal women tend to be on multiple medications for comorbid conditions.[24]

Behavior-based interventions such as cognitive behavioral therapy (CBT) have shown to be effective not only for depression but also for the management of other menopause-related problems, including anxiety, sleep problems, and VMS.[58,59] Evidence shows that patients are more likely to adhere to treatments and have more favorable outcomes when provided with choices to pursue medication, behavioral therapies, or both.[60]

γ-Aminobutyric Acid Type A Modulators

With the increasing evidence of the role of GABAergic systems for the development of depression and anxiety, a greater attention has been paid to the potential value of neurosteroids such as allopregnanolone for the management of these conditions, given it can positively modulate γ-aminobutyric acid type A (GABAA) receptors. Enhancing the inhibitory effects on GABAA receptors may lead to rapid decreases in anxiety levels and reduction in depression symptoms.

Among those, zuranolone and brexanolone are promising treatments due to their effects as positive allosteric modulators of GABAA receptors—brexanolone is already Food and Drug Administration–approved for the management of postpartum depression,[61] whereas zuranolone is in late stage of clinical development.[62] It remains to be seen whether the antidepressant properties of GABAA modulators will be further applied to midlife-related mood and anxiety symptoms.

SUMMARY

The transition to menopause and early postmenopausal years may be quite challenging for some women, with the increased risk for developing depressive symptoms (new, recurrent) and anxiety, along with vasomotor complaints, sleep problems, and other menopause-related health conditions. It is fundamental that health professionals providing care for women during midlife years are prepared to recognize this window of vulnerability and to manage it accordingly. Importantly, neither depression nor

anxiety during midlife years should be managed in isolation. Sleep problems, cognitive complaints, sexual dysfunction as well as the occurrence of context-related life stressors should be taken into consideration for the development of comprehensive, effective treatment plans.

It is now well established that estrogen plays an important neuromodulatory role—on the one hand, E2 fluctuations may contribute to the emergence of depression and anxiety symptoms; on the other hand, E2-based therapies may in fact alleviate these conditions, particularly when administered to symptomatic women in the menopausal transition and early postmenopausal years and/or experiencing increasing anxiety and stress during times of intense E2 fluctuations.

Antidepressants and behavioral therapies remain, however, the treatments of choice for depression and anxiety across the life span, including midlife years.

CLINICS CARE POINTS

- Some women may experience a 'window of vulnerability' for the development of mood and anxiety symptoms during the menopause transition.
- The presence and severity of vasomotor symptoms, sleep disturbances and cognitive changes should be taken into consideration when reviewing treatment options for symptomatic midlife women suffering from depression.
- Evidence-based treatments include pharmacologic, hormonal and behavioural options; treament should be tailored to patients' needs, taking into account efficacy, safety and tolerability.

DISCLOSURE

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REFERENCES

1. Rehm J, Shield KD. Global Burden of Disease and the Impact of Mental and Addictive Disorders. Curr Psychiatry Rep 2019;21(2):10.
2. Available at: https://www.who.int/news-room/fact-sheets/detail/depression. Consulted on September 24, 2022.
3. Available at: https://www.who.int/news/item/02-03-2022-covid-19-pandemic-triggers-25-increase-in-prevalence-of-anxiety-and-depression-worldwide. Consulted on October 1, 2022.
4. Ettman CK, Fan AY, Subramanian M, et al. Prevalence of depressive symptoms in U.S. adults during the COVID-19 pandemic: A systematic review. SSM Popul Health 2023;21:101348.
5. Hessami K, Romanelli C, Chiurazzi M, et al. COVID-19 pandemic and maternal mental health: a systematic review and meta-analysis. J Matern Fetal Neonatal Med 2022;35(20):4014–21.
6. Wong E, Franceschini N, Tinker LF, et al. Continuity of Care Among Postmenopausal Women With Cardiometabolic Diseases in the United States Early During the COVID-19 Pandemic: Findings From the Women's Health Initiative. J Gerontol A Biol Sci Med Sci 2022;77(Suppl 1):S13–21.

7. Soares CN, Zitek B. Reproductive hormone sensitivity and risk for depression across the female life cycle: a continuum of vulnerability? J Psychiatry Neurosci 2008;33(4):331–43.
8. Nolan LN, Hughes L. Premenstrual exacerbation of mental health disorders: a systematic review of prospective studies. Arch Womens Ment Health 2022; 25(5):831–52.
9. Eisenlohr-Moul TA, Schmalenberger KM, Owens SA, et al. Perimenstrual exacerbation of symptoms in borderline personality disorder: evidence from multilevel models and the Carolina Premenstrual Assessment Scoring System. Psychol Med 2018;48(12):2085–95 [published correction appears in Psychol Med. 2018 Sep;48(12):2100].
10. Yan H, Ding Y, Guo W. Suicidality in patients with premenstrual dysphoric disorder-A systematic review and meta-analysis. J Affect Disord 2021;295: 339–46.
11. Soares CN. Mood disorders in midlife women: understanding the critical window and its clinical implications. Menopause 2014;21(2):198–206.
12. Kase NG, Gretz Friedman E, Brodman M, et al. The midlife transition and the risk of cardiovascular disease and cancer I: magnitude and mechanisms. Am J Obstet Gynecol 2020;223(6):820–33.
13. El Khoudary SR, Greendale G, Crawford SL, et al. The menopause transition and women's health at midlife: a progress report from the Study of Women's Health Across the Nation (SWAN). Menopause 2019;26(10):1213–27.
14. Pietrzak RH, Kinley J, Afifi TO, et al. Subsyndromal depression in the United States: prevalence, course, and risk for incident psychiatric outcomes. Psychol Med 2013;43(7):1401–14.
15. Bromberger JT, Matthews KA, Schott LL, et al. Depressive symptoms during the menopausal transition: the Study of Women's Health Across the Nation (SWAN). J Affect Disord 2007;103(1–3):267–72.
16. de Kruif M, Spijker AT, Molendijk ML. Depression during the perimenopause: A meta-analysis. J Affect Disord 2016;206:174–80.
17. Cohen LS, Soares CN, Vitonis AF, et al. Risk for new onset of depression during the menopausal transition: the Harvard study of moods and cycles. Arch Gen Psychiatry 2006;63(4):385–90.
18. Bromberger JT, Kravitz HM. Mood and menopause: findings from the Study of Women's Health Across the Nation (SWAN) over 10 years. Obstet Gynecol Clin North Am 2011;38(3):609–25.
19. Shea AK, Sohel N, Gilsing A, et al. Depression, hormone therapy, and the menopausal transition among women aged 45 to 64 years using Canadian Longitudinal Study on aging baseline data. Menopause 2020;27(7):763–70.
20. Bromberger JT, Schott L, Kravitz HM, et al. Risk factors for major depression during midlife among a community sample of women with and without prior major depression: are they the same or different? Psychol Med 2015;45:1653–64.
21. Freeman EW, Sammel MD, Lin H, et al. Associations of hormones and menopausal status with depressed mood in women with no history of depression. Arch Gen Psychiatry 2006;63:375–82.
22. Gordon JL, Rubinow DR, Eisenlohr-Moul TA, et al. Estradiol variability, stressful life events, and the emergence of depressive symptomatology during the menopausal transition. Menopause 2016;23(3):257–66.
23. Bromberger JT, Kravitz HM, Youk A, et al. Patterns of depressive disorders across 13 years and their determinants among midlife women: SWAN mental health study. J Affect Disord 2016;206:31–40.

24. Soares CN, Shea AK. The Midlife Transition, Depression, and Its Clinical Management. Obstet Gynecol Clin North Am 2021;48(1):215–29.
25. McEwen BS, Alves SE. Estrogen actions in the central nervous system. Endocr Rev 1999;20(3):279–307.
26. Lokuge S, Frey BN, Foster JA, et al. Depression in women: windows of vulnerability and new insights into the link between estrogen and serotonin. J Clin Psychiatry 2011;72(11):e1563–9.
27. Rubinow DR, Johnson SL, Schmidt PJ, et al. Efficacy of estradiol in perimenopausal depression: so much promise and so few answers. Depress Anxiety 2015;32(8):539–54.
28. Cyr M, Bosse R, Di Paolo T. Gonadal hormones modulate 5-hydroxytryptamine2A receptors: emphasis on the rat frontal cortex. Neuroscience 1998;83(3):829–36.
29. Hiroi R, McDevitt RA, Neumaier JF. Estrogen selectively increases tryptophan hydroxylase-2 mRNA expression in distinct subregions of rat midbrain raphe nucleus: association between gene expression and anxiety behavior in the open field. Biol Psychiatry 2006;60(3):288–95.
30. Pau KY, Hess DL, Kohama S, et al. Oestrogen upregulates noradrenaline release in the mediobasal hypothalamus and tyrosine hydroxylase gene expression in the brainstem of ovariectomized rhesus macaques. J Neuroendocrinol 2000;12(9):899–909.
31. Srivastava DP, Woolfrey KM, Evans PD. Mechanisms underlying the interactions between rapid estrogenic and BDNF control of synaptic connectivity. Neuroscience 2013;239:17–33.
32. Schmidt PJ, Ben Dor R, Martinez PE, et al. Effects of estradiol withdrawal on mood in women with past perimenopausal depression: a randomized clinical trial. JAMA Psychiatr 2015;72:714–26.
33. Schweizer-Schubert S, Gordon JL, Eisenlohr-Moul TA, et al. Steroid Hormone Sensitivity in Reproductive Mood Disorders: On the Role of the $GABA_A$ Receptor Complex and Stress During Hormonal Transitions. Front Med 2021;7:479646.
34. Schiller CE, Johnson SL, Abate AC, et al. Reproductive steroid regulation of mood and behavior. Compr Physiol 2016;6:1135.
35. Kanes S, Colquhoun H, Gunduz-Bruce H, et al. Brexanolone (SAGE-547 injection) in post-partum depression: a randomised controlled trial. Lancet 2017;390:480–9.
36. Slopien R, Pluchino N, Warenik-Szymankiewicz A, et al. Correlation between allopregnanolone levels and depressive symptoms during late menopausal transition and early postmenopause. Gynecol Endocrinol 2018;34:144–7.
37. Schmidt PJ, Nieman L, Danaceau MA, et al. Estrogen replacement in perimenopause-related depression: a preliminary report. Am J Obstet Gynecol 2000;183(2):414–20.
38. Soares CN, Almeida OP, Joffe H, et al. Efficacy of estradiol for the treatment of depressive disorders in perimenopausal women: a double-blind, randomized, placebo-controlled trial. Arch Gen Psychiatry 2001;58(6):529–34.
39. 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.
40. Morrison MF, Kallan MJ, Ten Have T, et al. Lack of efficacy of estradiol for depression in postmenopausal women: a randomized, controlled trial. Biol Psychiatry 2004;55(4):406–12.

41. Maki PM, Kornstein SG, Joffe H, et al. Guidelines for the evaluation and treatment of perimenopausal depression: summary and recommendations. Menopause 2018;25(10):1069–85.
42. Manson JE, Bassuk SS, Kaunitz AM, et al. The Women's Health Initiative trials of menopausal hormone therapy: lessons learned. Menopause 2020;27(8):918–28.
43. Gordon JL, Rubinow DR, Eisenlohr-Moul TA, et al. Efficacy of Transdermal Estradiol and Micronized Progesterone in the Prevention of Depressive Symptoms in the Menopause Transition: A Randomized Clinical Trial. JAMA Psychiatr 2018; 75(2):149–57.
44. Bromberger JT, Kravitz HM, Chang Y, et al. Does risk for anxiety increase during the menopausal transition? Study of women's health across the nation. Menopause 2013;20(5):488–95.
45. Freeman EW, Sammel MD. Anxiety as a risk factor for menopausal hot flashes: evidence from the Penn Ovarian Aging Cohort. Menopause 2016;23(90):942–9.
46. Enomoto H, Terauchi M, Odai T, et al. Independent association of palpitation with vasomotor symptoms and anxiety in middle-aged women. Menopause 2021; 28(7):741–7.
47. Lozza-Fiacco S, Gordon JL, Andersen EH, et al. Baseline anxiety-sensitivity to estradiol fluctuations predicts anxiety symptom response to transdermal estradiol treatment in perimenopausal women.A randomized clinical trial. Psychoneuroendocrinology 2022;143:105851.
48. Freeman MP, Cheng LJ, Moustafa D, et al. Vortioxetine for major depressive disorder, vasomotor, and cognitive symptoms associated with the menopausal transition. Ann Clin Psychiatry 2017;29(4):249–57.
49. Frey BN, Haber E, Mendes GC, et al. Effects of quetiapine extended release on sleep and quality of life in midlife women with major depressive disorder. Arch Womens Ment Health 2013;16(1):83–5.
50. Gambacciani M, Ciaponi M, Cappagli B, et al. Effects of low-dose, continuous combined estradiol and noretisterone acetate on menopausal quality of life in early postmenopausal women. Maturitas 2003;44(2):157–63.
51. Joffe H, Groninger H, Soares CN, et al. An open trial of mirtazapine in menopausal women with depression unresponsive to estrogen replacement therapy. J Womens Health Gend Based Med 2001;10(10):999–1004.
52. Joffe H, Soares CN, Petrillo LF, et al. Treatment of depression and menopause-related symptoms with the serotonin-norepinephrine reuptake inhibitor duloxetine. J Clin Psychiatry 2007;68(6):943–50.
53. Kornstein SG, Jiang Q, Reddy S, et al. Short-term efficacy and safety of desvenlafaxine in a randomized, placebo-controlled study of perimenopausal and postmenopausal women with major depressive disorder. J Clin Psychiatry 2010;71(8): 1088–96.
54. Soares CN, Kornstein SG, Thase ME, et al. Assessing the efficacy of desvenlafaxine for improving functioning and well-being outcome measures in patients with major depressive disorder: a pooled analysis of 9 double-blind, placebocontrolled, 8-week clinical trials. J Clin Psychiatry 2009;70(10): 1365–71.
55. Soares CN, Thase ME, Clayton A, et al. Desvenlafaxine and escitalopram for the treatment of postmenopausal women with major depressive disorder. Menopause 2010;17(4):700–11.
56. Soares CN, Frey BN, Haber E, et al. A pilot, 8-week, placebo lead-in trial of quetiapine extended release for depression in midlife women: impact on

mood and menopause-related symptoms. J Clin Psychopharmacol 2010;30(5):612–5.
57. Zhou J, Wang X, Feng L, et al. Venlafaxine vs. fluoxetine in postmenopausal women with major depressive disorder: an 8-week, randomized, single-blind, active-controlled study. BMC Psychiatr 2021;21(1):260.
58. Green SM, Donegan E, McCabe RE, et al. Objective and subjective vasomotor symptom outcomes in the CBT-Meno randomized controlled trial. Climacteric 2020;23(5):482–8.
59. Diem SJ, LaCroix AZ, Reed SD, et al. Effects of pharmacologic and nonpharmacologic interventions on menopause-related quality of life: a pooled analysis of individual participant data from four MsFLASH trials. Menopause 2020;27(10):1126–36.
60. McCurry SM, Guthrie KA, Morin CM, et al. Telephone-Based Cognitive Behavioral Therapy for Insomnia in Perimenopausal and Postmenopausal Women With Vasomotor Symptoms: A MsFLASH Randomized Clinical Trial. JAMA Intern Med 2016;176(7):913–20.
61. Edinoff AN, Odisho AS, Lewis K, et al. Brexanolone, a $GABA_A$ Modulator, in the Treatment of Postpartum Depression in Adults: A Comprehensive Review. Front Psychiatry 2021;12:699740.
62. Gunduz-Bruce H, Silber C, Kaul I, et al. Trial of SAGE-217 in Patients with Major Depressive Disorder. N Engl J Med 2019;381(10):903–11.