Depression and Menopause

An Update on Current Knowledge and Clinical Management for this Critical Window

Claudio N. Soares, MD, PhD, FRCPC, MBA[a,b,*]

KEYWORDS

• Depression • Menopause • Hot flashes • Anxiety • Sleep
• Estrogen therapy and mood regulation • Nonhormonal interventions

KEY POINTS

- Depression is a disabling condition, which often leads to significant personal, societal, and economic costs.
- Windows of vulnerability for depression likely are associated with an increased sensitivity to changes in the hormonal milieu experienced by some (but not all) women during the luteal phase of their cycles, the postpartum period, and/or during the menopause transition.
- An increased awareness of those windows of vulnerability has resulted in greater adoption of screening tools for mood and behavioral changes and tailored therapies for postpartum-related depressive episodes.
- Therapies uniquely designed for menopause-related depression are still debated. Part of the controversy has derived from conflicting methodologies to characterize reproductive staging or assess psychiatric conditions, and different targeted populations identified and assessed for the efficacy and tolerability of various antidepressant treatments, hormone therapies, or other interventions.

INTRODUCTION

Depression is a disabling condition that affects more than 300 million people worldwide and often leads to significant personal, societal, and economic costs. It affects 1 in every 5 adults in North America, with women being disproportionately more

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[a] Department of Psychiatry, Queen's University School of Medicine, 752 King Street West, Kingston, Ontario K7L 4X3, Canada; [b] Research and Innovation, Providence Care Hospital, Kingston, Ontario, Canada
* Department of Psychiatry, Queen's University School of Medicine, 752 King Street West, Kingston, Ontario K7L 4X3, Canada.
E-mail address: c.soares@queensu.ca

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affected than men. Such an increased risk (2-fold on average) has been the subject of debate and research over the years and from different viewpoints, including epidemiology, genetics, socioeconomic determinants of health, coping strategies, and hormone variations.[1,2]

Several researchers have been instrumental in proposing a paradigm to examine why some (but not all) women would be more likely to experience greater vulnerability for depression at certain stages (or windows) across the lifespan.[3–7] Based on this paradigm, the notion of windows of vulnerability for depression, also known as reproductive-related depressive episodes, was postulated to describe an increased sensitivity experienced by some women to changes in the hormonal milieu that occur during the luteal phase of their cycles, during the postpartum period, and/or during the menopause transition.

There has been an increased awareness of those windows of vulnerability, which is reflected in greater adoption of screening tools for mood and behavioral changes in the postpartum period, as well as the recognition by the American Psychiatric Association of the severity and functional impairment associated with the occurrence of premenstrual dysphoric disorder (PMDD). This has led to the inclusion of PMDD as a diagnostic category in the *Diagnostic and Statistical Manual of Mental Disorders*, *5th edition*. Likewise, researchers and clinicians have developed therapeutic strategies tailored to reproductive-related mood events such as postpartum depression.[8]

The existence of a menopause-associated depression has been a more controversial point, despite undeniable evidence that this stage in life might be accompanied by other medical conditions, cardiovascular issues, vasomotor symptoms, sleep problems, and stressful life events, just to name a few.[9] The controversy has been fueled by conflicting methodologies used to characterize reproductive staging or assess psychiatric conditions in various studies, and by the scarcity of trials in which this targeted population (midlife women with depression and well-characterized menopause staging) was properly ascertained and assessed for the efficacy and tolerability of various antidepressant treatments, hormone therapies, or other interventions.

Depression and Menopause: Some Facts and Guiding Principles

The heightened burden associated with a major depressive disorder (MDD) is undeniable at any given point in the life cycle. However, the occurrence and persistence of depressive symptoms (not fully meeting criteria for clinical depression) may also lead to psychosocial impairment and adversely affect overall health.[10,11] Therefore, it is important that clinicians keep a closer monitoring and periodically reassess the need for therapies to address bothersome depressive symptoms (eg, low mood, reduced motivation and enjoyment with usual activities, disrupted sleep) through the use of pharmacologic agents, behavioral or lifestyle changes, or other treatments.

Cross-sectional and prospective studies have now investigated a potential association between menopause staging and the risks for depressive symptoms or MDD (new onset or recurrent).[12] Overall, data from cross-sectional studies indicate that depressive symptoms might be endorsed by up to 70% of women during perimenopause compared with around 30% in premenopausal years. Longitudinal studies, perhaps representing a better strategy for the assessment of this potential association, have suggested an increased risk of 1.5-fold to 3.0-fold for the occurrence of depressive symptoms during the menopause transition.[13,14] Importantly, such increased risk was identified even among women with no previous episodes; that is,

new onset of symptoms. Finally, cohort studies have documented an increased risk for clinical depression (MDD, 2-fold to 4-fold increased risk) throughout the menopause transition and early postmenopausal years.

Risk factors for depression associated with the menopausal years can be grouped into 2 categories:

1. Continuum of risk factors: Longitudinal studies have identified risk factors for the occurrence of midlife depression that seem pervasive throughout the lifespan; these constitute a continuum of risk for depression and most likely act as moderating factors. These factors could be characterized as demographic or socioeconomic (ie, unemployment, low education, being black or Hispanic), health-related (eg, greater body mass index, being a smoker, reporting poor health and impaired functioning due to chronic medical conditions), and psychosocial (eg, poor social support, history of anxiety, 1 or more stressful life events). Importantly, a previous depressive episode is the strongest predictor for depression during midlife years, whereas a history of mood symptoms with a hormone-related context (ie, history of premenstrual syndrome, PMDD, or postpartum depression) has been moderately linked to depressive symptoms during the menopause transition and early postmenopausal years.
2. Window of risk–related factors: Researchers have also investigated the role of timing-related, context-related factors. Again, data from cross-sectional and longitudinal studies were valuable sources and helped identify mediating or precipitating factors associated with menopause-related depression. These factors include hormone variations (ie, the experience of wider fluctuations in follicle-stimulating hormone [FSH] and estradiol [E2] levels over time), menopause-related symptoms (eg, the presence and severity of vasomotor symptoms, sleep problems), overall health (current poor health, low functioning due to chronic medical conditions), and psychosocial stressors (including poor social support and stressful life events). The latter is characterized not only by the magnitude and number of events but also based on the temporal proximity (ie, timing of their occurrence in relation to the menopause transition per se).

Long-term trajectories

More recent studies have taken a closer look at prospective data to determine mediators for distinct trajectories of depressive symptoms throughout the menopause transition and beyond. The Study of Women's Health Across the Nation (SWAN) used data from a 13-year follow-up period to examine the course of clinical depression. The SWAN investigators determined that about 30% of those who developed depression at some point during the study ultimately experienced evolution into a persistent or recurrent condition. This was true even among those with new-onset cases of depression. Sleep problems and recent upsetting life events were among contributing factors to more persistent and/or recurrent depressive outcomes.[15,16] The Australian Longitudinal Study on Women's Health, on the other hand, identified 4 distinct patterns for depressive symptoms over a 15-year follow-up based on changes in the Center for Epidemiologic Studies Depression Scale (CES-D) scores over time: stable low (80.0%), increasing scores (9.0%), decreasing scores (8.5%), and stable high (2.5%). Those exhibiting stable high or increasing depressive symptoms over time (around 10%) were likely to experience continuum of risk factors such as previous diagnosis or treatment of depression and socioeconomic challenges. There were also context-related risk factors such as the exposure to a prolonged perimenopause or a surgically induced menopause.[17]

The role of anxiety and sleep

Anxiety and sleep problems are often identified as contributing factors to greater psychiatric morbidity among midlife women. Anxiety disorders constitute a heterogeneous group in which comorbid conditions are quite common and symptoms may overlap considerably. SWAN investigators attempted to explore 4 components or symptoms of anxiety (irritability, nervousness or tension, feeling fearful for no reason, and heart pounding or racing) and categorized their occurrence as high or low anxiety based on their scoring on the General Anxiety Disorder-7 scale.[18] They also examined whether anxiety symptoms at study entry would be more likely or less likely to occur during or after the menopausal transition than in their premenopausal years, regardless of the presence of vasomotor symptoms, health factors, or psychosocial stressors. Overall, women with high anxiety symptoms at study entry maintained significant rates of anxiety (16%–21%) throughout the 10-year follow-up period. Interestingly, the percentage of documented high anxiety visits declined from 71.4% (occurring during premenopausal years) to 30.0% (in the postmenopausal period). Moreover, those who reported high anxiety at baseline experienced a peak in symptoms during late perimenopausal years (13.5%), which is a much higher percentage than those observed in premenopausal years (4.6%), suggesting a possible window of vulnerability for increased anxiety in some women during midlife years.

More recently, Freeman and Sammel[19] (2016) examined the association between anxiety and severity of hot flashes over a 14-year follow-up interval (Penn Ovarian Aging Cohort). Somatic anxiety was strongly associated with hot flashes in the menopause transition, even after adjusting for important factors such as age, menopausal staging, reproductive hormone levels, history of depression, and others. Importantly, rather than cooccurring with vasomotor symptoms, somatic anxiety actually predicted the risk of further developing moderate or severe hot flashes.

Clinicians and patients often question whether sleep problems in midlife years represent a primary condition or an expression of an underlying problem (eg, presence of vasomotor symptoms or depression). Kravitz and colleagues[20] investigated possible interactions between menopause changes and sleep, and found an association between changes in bleeding patterns during the menopause transition and the emergence of sleep disturbances. Others indicated that women experiencing depression and vasomotor symptoms are likely to report poorer perceived sleep quality despite the lack of objective measures of sleep disruption; that is, an actual increase in number of awakenings or night sweats, or even significant changes in wakefulness after sleep onset (WASO) time.[21,22]

Joffe and colleagues[23] submitted 39 healthy, premenopausal women to gonadal hormone suppression by administering leuprolide to examine the independent contribution of hot flashes and sleep disturbances to the emergence of depressive symptoms among estrogen-deprived women. After 4 weeks of leuprolide use, 20 women (69%) developed hot flushes, whereas only 1 subject developed clinical depression. The increase in depressive symptoms (Montgomery-Åsberg Depression Rating Scale [MADRS] scores) was associated with objective and subjective changes in sleep patterns. However, only nocturnal hot flashes (and not daytime vasomotor symptoms) seemed to be significantly associated with an increase in depressive symptoms, even after adjusting for changes on sleep, suggesting that disturbed sleep does not fully explain the association of nocturnal hot flashes and mood disturbance in women experiencing estrogen depletion due to surgical or natural menopause.

Lampio and colleagues[24] (2016) examined the effects of aging and menopausal hormonal changes on sleep architecture during the menopause transition (6-year follow-up). The investigators collected overnight polysomnography recordings at

baseline and at the follow-up visit, as well as FSH levels over time. Both aging and increased FSH concentration had an impact on sleep architecture. The age-related changes included shorter total sleep time, lower sleep efficiency, and greater sleep fragmentation; for example, increased WASO. Clinical characteristics and increased FSH levels (a marker of transition from premenopause to postmenopause) were associated with higher proportion of slow wave sleep and increased WASO.

WHAT ABOUT THE ESTROGEN CONNECTION?

Estrogen and Mood Regulation

The mediating effects of estrogen on monoaminergic systems, namely serotonin (5-hydroxytryptamine [5-HT]) and noradrenaline (NE) neurotransmission, may contribute to the development of depressive symptoms in women.[25–27] The presence and wide distribution of estrogen receptors in the brain and the estrogen activity found in regions known to be involved in mood and cognitive regulation (eg, prefrontal cortex, hippocampus) are contributing arguments to the notion that estrogen exerts mediating effects (and possibly therapeutic effects) on mood.[25,28,29]

Overall, the effects of E on 5-HT and NE could be characterized as beneficial to mood.[30] E2 administration limits the activity of monoamine oxidases (MAOs) A and B, which are enzymes involved in 5-HT degradation.[31] It also increases both isoforms of tryptophan hydroxylase, the rate-limiting enzyme of serotonin synthesis.[32,33] Thus, E2 administration results in an overall net increase in 5-HT synthesis and availability. Moreover, estrogens increased 5-HT receptor density in brain regions containing E receptors, such as the hypothalamus, the preoptic area, and the amygdala.[34–37] E2 downregulates $5HT_{1a}$ auto-receptors and upregulates $5HT_{2a}$ receptors, increasing the amount of serotonin found in the synapse and consequently the amount available for postsynaptic transmission. Estrogen effects also promote NE availability by decreasing the expression of MAOs and increasing the activity of tyrosine hydroxylase, the rate-limiting enzyme in the synthesis of catecholamine.[38,39] Acute E2 administration increases dopamine β-hydroxylase (DBH) gene transcription; DBH catalyzes the hydroxylation of dopamine to form NE. In sum, estrogen works via distinct pathways to regulate synthesis, metabolism, and receptor density or activity of the classical neurotransmitters implicated in mood regulation.[40,41] Finally, estrogen may also have mood-enhancing (or antidepressant-like) properties due to its stimulating effect on brain-derived neurotrophic factor, an important neuroprotective agent at multiple levels.[42]

Estrogen Therapy for Depression: Level I Evidence of a Critical Window

Despite some evidence of E2 antidepressant properties, particularly among depressed, perimenopausal women, the acceptability of estrogen therapy (ET) as part of the therapeutic armamentarium for depression remains limited. A recent, comprehensive systematic review examined the efficacy of estrogen-based interventions for depression.[30] Potentially relevant studies were selected based on the following criteria: (1) clinical administration of estrogen-based, hormone therapy and (2) assessment of mood symptoms or depression with standardized instruments.

Surprisingly, only a few randomized controlled trials (RCTs) have examined the benefits of ET on clinically depressed women. Most studies included women who were either asymptomatic or mildly affected at study entry, again making it more difficult to generalize and/or compare their findings. Thus, given the scarce number of RCTs with estrogen-based therapies for menopause depression, the author has expanded the review conducted by Rubinow and colleagues and included open-label, single-blind, and double-blind interventions.

The author also recognizes that clinical trials have not been the only source of information for a better understanding of the effects of estrogen on mood. Some have explored the brain-related effects of estrogen in longitudinal observational studies; for example, by comparing women who underwent oophorectomy before the onset of menopause (average follow-up 25 years) to an aged-matched sample from the same community; a particular study demonstrated that those who underwent surgery had a significant increased risk for developing depressive and anxiety symptoms when compared with the referent group.[43] The risks were even greater among those who underwent surgery at younger age, leading the author to speculate a potential association of these findings with an early loss of neuroprotective effects of estrogen during reproductive years.

Mood Regulation: Estrogen Therapies in Nondepressed Women

Perimenopausal women

A single RCT assessed mood in strictly nondepressed, perimenopausal women (N = 83, aged 40–52 years).[44] Menopausal staging was based on menstrual patterns and the presence of vasomotor symptoms, whereas depressive symptoms were assessed via a standardized instrument: the Zung Self Rating Depression Scale. This was a 6-month, crossover study comparing a hormone treatment (estrogen-progestin therapy [EPT]) with 2 weeks of conjugated equine estrogen (CEE) followed by 2 weeks of CEE plus medroxyprogesterone acetate (MPA). No significant effects on mood were observed when the order of treatment allocation was ignored. Study limitations included the lack of a calibration or run-in period, and the treatment duration.

In a recent pilot study of perimenopausal women (N = 38, aged 38–52 years) who were predominantly nondepressed, the investigators compared the effects of levonorgestrel-containing intrauterine system (LNG-IUS) plus low-dose transdermal E2 (gel 0.06% containing 0.75 mg E2 per 1.25 g metered dose) to LNG-IUS alone (plus inactive gel) for 50 days. The study assessed depressive symptoms using the CES-D, the impact of hot flashes using the Hot Flash–Related Daily Interference Scale, fatigue using the Fatigue Severity Scale, and sleep characteristics via the Pittsburgh Sleep Quality Index. Although most women were symptomatic with respect to hot flashes (61%) and poor sleep (71%), only a small number reported significant depressive symptoms (CES-D scores >16, n = 5 or 13%) or fatigue (n = 5, 13%) at study entry. Overall, the study revealed beneficial effects of LNG-IUS plus TDE for the improvement of hot flashes and daytime fatigue, with minimal or nonsignificant effects on sleep and no significant changes in mood (improvement or worsening).[45]

To date, only 1 randomized trial has investigated the efficacy of estrogen in preventing the onset of significant depressive symptoms in perimenopausal and early postmenopausal women. Euthymic perimenopausal or early postmenopausal women (n = 172) were assigned to receive either transdermal E2 (0.1 mg/d) plus intermittent oral micronized progesterone (200 mg/d for 12 days every 3 months) or placebo patches plus pills. After 12 months, women receiving active HT were significantly less likely to develop depressive symptoms compared with women receiving placebo (32.3% vs 17.3%). Those in the early perimenopausal stage (but not late perimenopausal or early postmenopausal stages) benefited the most from estrogen as a preventive strategy. The benefits were also modified by stressful life events, with greater benefits for women who had experienced stressful life events in the preceding 6 months of the intervention. Vasomotor symptoms and prior history of MDD did not modify the effect of HT on depressive symptoms. These findings, if further replicated, highlight the importance of a careful clinical interview to facilitate personalized interventions for midlife women.

Postmenopausal women

The effects of HT on mood have been assessed in clinical studies in younger, postmenopausal women (ie, up to 10 years postmenopause and aged <70 years). In most studies, the presence of menopause-related symptoms (ie, vasomotor, sleep, pain) was documented at study entry, making the alleviation of these symptoms with hormone interventions an important factor (mediating and/or confounding) to be considered. Haines and colleagues[46] (2003) studied 152 postmenopausal women (posthysterectomy, aged 48 ± 5 years) in a randomized, double-blind placebo-controlled trial of 1 or 2 mg of oral E2 or placebo for 12 months (primary outcome: prevention of bone loss, ie, reduced risk for osteoporosis). Women had their depressive symptoms assessed via the Hospital Anxiety and Depression Scale and their psychological wellbeing and quality of life (QOL) using the World Health Organization QOL questionnaire. Over a 12-month follow-up period, menopausal symptoms were significantly reduced in the 2 mg arm (not among those using 1 mg or placebo), whereas no significant changes in mood or QOL were observed (from mild or no significant impairment observed at baseline).

Fifty-four asymptomatic postmenopausal women (average age 52 ± 4 years) were randomized to receive oral ET (CEE 0.625 mg/d), EPT (CEE + MPA, 10 mg/d), or placebo in a 6-month trial. Subjects were recruited based on the absence of psychiatric symptoms (HAM-D and HAM-A scales) and assessed at baseline and endpoint for psychological symptoms using the Beck Depression Inventory (BDI) and the Profile of Moods States. Hormone treatment did not lead to a significant change in mood over time when compared with placebo.[47]

In another trial (3-month duration), 183 postmenopausal women (average age 48 years, postmenopausal for at least 1 year) were recruited based on the presence of severe menopausal symptoms and randomized into 3 treatment groups: (1) transdermal E2 plus oral norethisterone acetate, (2) oral continuous combination of norethisterone and E2 hemihydrate, or (3) placebo. Menopausal, depressive, and anxiety symptoms were assessed using the Kupperman scale, the Hamilton Depression Rating Scale (HDRS), and the Beck Anxiety Inventory (BAI), respectively. Compared with placebo, the use of transdermal E2 (alone or in combination with norethisterone) led to a significant improvement of menopausal symptoms, as well as reduction in HDRS and BAI scores depression and anxiety symptoms.[48]

Almeida and colleagues[49] examined the benefits of ET (oral E2, 2 mg/d) for cognition, mood, and QOL in older postmenopausal women (n = 115, average age 73 years) in a 20-week randomized double-blind placebo-controlled trial. Outcome measures included changes in the BDI, changes in QOL scores (SF-36), and cognitive function (CAMCOG, Block Design, Memory for Faces, California Verbal Learning Test, and verbal fluency). After 20 weeks of treatment, unopposed estrogen administered orally was not associated with significant changes in cognitive function, mood, or QOL.

In another placebo-controlled trial, 412 postmenopausal women (average age 71 years) were allocated into 4 different treatment groups: ET with 0.625 of CEE, CEE plus 2.5 mg of MPA, calcitriol 0.25 g twice a day alone, and a combination of HT and calcitriol. Depression symptoms were assessed via the Geriatric Depression Scale (GDS) at baseline and at the end of the 36-month trial. GDS scores suggested that about 12% of the sample was depressed at study entry. No significant effects of hormone treatment on mood were observed at endpoint, and the percentage of depressed women (based on GDS scores) decreased across all treatment groups.[50]

In sum, these results suggest a lack of significant beneficial effects of estrogen on mood (ie, mood improvement) when administered to nondepressed women,

particularly in their postmenopausal years. Preliminary but promising results suggest a potential role for estrogen in mitigating the risk for developing depressive symptoms among specific at-risk subpopulations transitioning to menopause.

Additional information has been derived from large trials such as the Heart and Estrogen/Progestin Replacement Study (HERS),[51] the Women's Health Initiative Study of Cognitive Aging (WHISCA)[52,53] and the Women's International Study of long Duration Estrogen after the Menopause (WISDOM).[54,55] These studies offered additional opportunities to examine the effects of hormone therapies on mood and QOL among both younger and older nondepressed postmenopausal women. Altogether, these studies failed to demonstrate a significant impact of hormone therapies on mood and reiterate the notion that estrogen-based therapies should not be considered as a strategy for prevention or alleviation of mood symptoms in otherwise nondepressed, asymptomatic perimenopausal, or postmenopausal women.[30] Recent data from the Kronos Early Estrogen Prevention Study (KEEPS) examined the effects of estrogen-based therapies on mood symptoms among nondepressed, early postmenopausal women.[56,57] Contrary to other studies, the investigators identified a positive impact on mood with the use of oral CEEs but not with transdermal E2.

Mood Improvement: The Use of Estrogen Therapies in Depressed Women

Perimenopausal women

At least 4 small studies, including 2 RCTs, have demonstrated the efficacy of E2 for the management of depressive disorders during perimenopause.[58–61] The 2 RCTS (Soares and Schmidt) had similar designs and are considered of high quality due to the utilization of standardized tools to confirm the diagnosis of depression and the characterization of menopausal staging using FSH levels and history of menstrual irregularity. In addition, treatment compliance was monitored by serum E2 measurements in both studies. Antidepressant effects were well-documented (reduction in CES-D, HDRS, and MADRS scores) and significant mood improvement was observed among those suffering from new-onset or recurrent MDD in the presence or absence of concomitant vasomotor symptoms. Moreover, the antidepressant effects of E2 persisted after a 4-week washout period, even after reemergence of hot flashes and night sweats.[61]

Estrogen has also been used as an augmentation strategy for women with unsatisfactory response to antidepressants. Most studies suggest that estrogen might augment clinical response to antidepressants, including selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitor (SNRIs).[62–68]

Postmenopausal women

Two RCTs have assessed the use of hormone therapy in postmenopausal women with depressive disorders. Morrison and colleagues (2004) examined the efficacy of transdermal E2 (0.1 mg) compared with placebo in late postmenopausal women (N = 57; average age 67 years, postmenopausal for about 16 years) suffering from mild-to-moderate depression. After 8 weeks of treatment, both groups showed similar decrease in depressive symptoms based on changes in HDRS scores or self-assessed CES-D scores from baseline. The study also suggested that a subgroup of depressed postmenopausal women (ie, those with a past history of major depression) could be particularly responsive to placebo.

In another RCT, Rudolph and colleagues (2004) examined the effects of oral HT (a continuous combination of E2 valerate 2 mg and dienogest 2 mg/d) in a 24-week trial of 129 postmenopausal women. In this study, women were considerably younger (average age 55 years) and the use of HT led to significant improvements in depressive

scores (reduction in HDRS scores). These findings, however, should be examined with caution given the unusually high dropout rates observed among treatment users (33%) and placebo users (58%).

Finally, an RCT included 72 women with depression and was confirmed by the Structured Clinical Interview for Axis I Disorders of mild to moderate severity (ie, MADRS) scores of 15 to 31 at study entry. Women were perimenopausal and postmenopausal (mean age 51.1 $\pm$ 5.0 years), experiencing sleep disturbances (insomnia syndrome) that affected their functioning and reporting 3 or more nights per week with significant hot flashes. Subjects were randomly assigned to transdermal 17β-E2 0.05 mg/d, zolpidem 10 mg/d, or placebo for 8 weeks. All groups showed improvement in depressive symptoms (MADRS scores); that is, the study failed to demonstrate meaningful differences between active treatment groups and placebo. Interestingly, overall improvement in mood was significantly correlated with an increase in serum E2 over time and improvement in perceived quality. It is plausible that an increase in E2 levels occurred due to ET use in 1 treatment arm and/or to naturally occurring fluctuations among study participants. Mood improvement, however, was not significantly correlated with suppression of hot flashes or changes in objectively measures of sleep.[69]

Schmidt and colleagues[70] tested the estrogen withdrawal theory (previously examined in premenstrual and postnatal populations) in asymptomatic postmenopausal women (N = 56) with history of perimenopausal depression. After 3 weeks of open-label administration of transdermal E2 (100 μg/d), study participants were randomized to receive either E2 or matched placebo skin patches for 3 additional weeks in a double-blind fashion. There were no reports of depressive symptoms during the open-label phase with E2. Women with history of perimenopausal depression who were crossed over from E2 to placebo reported an increase in depressive symptoms (assessed by the CES-D and HDRS), whereas those (also with past history of perimenopausal depression) who remained on E2 therapy continued to be asymptomatic. Of note, both groups had similar hot-flush severity and plasma E2 levels while on placebo. The study by Schmidt and colleagues[70] elegantly demonstrated that some midlife women could be particularly susceptible to developing behavioral or mood changes when exposed to changes in estrogen levels or secretion. These findings corroborate the notion of a critical timing to consider estrogen's role as a contributing and/or mitigating factor for depression in midlife women.

In sum, ET, particularly transdermal E2, has shown antidepressant effects of similar magnitude to that observed with classic antidepressant agents when administered to perimenopausal women suffering from clinical depression, whereas it seems to be ineffective as a mood enhancer among depression-free (asymptomatic) women. Transdermal 17β-E2 seems to lead to a greater antidepressant effect size (ie, drug-placebo difference) and could therefore constitute a potential treatment of depressed mood in this population.[71,72] On the other hand, the same hormone intervention formulation (E2) and route of administration (transdermally) was not effective in treating depressed postmenopausal women.[73,74] This particular finding suggests that the menopausal transition might not only be a critical window of risk for depression but also a window of opportunity for the effective use of estrogen therapies for depression in midlife years.[9] However, existing data on estrogen-based therapies for depressed perimenopausal and postmenopausal women are limited in terms of number of randomized trials, sample sizes recruited, and number of study completers (**Table 1**), making the interpretation and generalization or applicability of some of these findings more challenging.

Table 1
Randomized trials on estrogen therapies for symptomatic or depressed perimenopausal and postmenopausal women

Authors	Population Studied (Type, n)	Design	Intervention	Outcome Measures	Key Findings
Schmidt et al,[60] 2001	Perimenopause-related depression (n = 31)	DB, PL Parallel study followed by crossover, PL-controlled	ET (transdermal E2), followed by MPA	HDRS, CES-D scores	ET led to significant improvements in depressive symptoms (HDRS and CES-D scores)
Soares et al,[61] 2001	Perimenopause-related depression (n = 45)	DB, PL Parallel study	ET (transdermal E2)	MADRS scores	ET led to significant improvements in depressive symptoms (MADRS scores)
Rudolph et al,[75] 2004; Santoro,[76] 2005	Postmenopausal women with mild or moderate depressive symptoms (n = 129)	DB, PL Parallel study	EPT (oral E2 valerate + progestin [dienogest])	HDRS scores	EPT led to improvements in HDRS scores; high attrition rates in both groups
Morrison et al,[73] 2004	Postmenopausal women with depressive disorders (n = 57)	DB, PL Parallel study	ET (transdermal E2) followed by MPA	HDRS, CES-D scores	No differences with active treatment (both groups showed improvement)
Joffe et al,[69] 2011	Mixed perimenopausal and postmenopausal women with depressive symptoms, VMS and insomnia (n = 72)	DB, PL Parallel study	ET (transdermal E2), Zolpidem	MADRS, BDI, PSQI scores	No significant differences with respect to mood changes between treatment and PL groups

Abbreviations: DB, double-blind; PL, placebo; PSQI, Pittsburgh Sleep Quality Index.

FINAL CONSIDERATIONS AND RECOMMENDATIONS REGARDING ESTROGEN THERAPIES

There are indicators of windows of vulnerability for cardiovascular, mood, and cognitive conditions in midlife women; at the same time, the critical window hypothesis suggests the existence of a window of opportunity for the administration of E2 to symptomatic women across different systems or domains. Further investigation is needed to disentangle common underlying mechanisms.[77]

Clinicians should always consider the various treatment strategies available and determine the extent to which they can be tailored to address the multiple symptom domains for each patient. For example, based on the author's review and accumulated clinical experience, an argument can be made that perimenopausal women presenting with significant, bothersome menopausal symptoms (significant VMS) and concurrent depressive symptoms could benefit from an initial, brief trial (2–4 weeks) with transdermal E2 as a monotherapy to determine the benefits and tolerability of hormone treatment for the alleviation of both mood and menopausal symptoms. After that, the need for antidepressant use (monotherapy or concomitant use) could be reassessed. Obviously, women who experienced multiple depressive episodes in the past (not necessarily hormone-related), and women presenting with severe depressive symptoms and/or expressing suicidal ideation should always be evaluated and treated with more intensive, widely used antidepressant strategies.

The type of hormone treatment and route of administration should be carefully considered if alleviation of depression is an important goal. Different HT formulations (eg, transdermal E2 vs oral conjugated estrogens, E alone vs estrogen plus progestin therapies) should take into consideration not only the risks or benefits for bone and cardiovascular health but also for cognitive and mood functioning. So far, the evidence for the use of transdermal E2 for depression is more robust and reinforced by its absorption process (no hepatic first-pass effects) and overall safety profile.

WHAT ABOUT NONHORMONAL INTERVENTIONS?

Antidepressants remain the first-line treatment of depression during midlife years, particularly for those who experienced multiple depressive episodes in the past (not necessarily hormone-related), reporting severe symptoms or significant functional impairment, and/or expressing suicidal ideation. For recurrent episodes, a previous response to a specific antidepressant (agent, class) should guide the primary decision on what to try first. For those experiencing depression for the first time, those who are treatment-naïve, or those presenting with history of partial or no response to antidepressants past, existing data support the efficacy and tolerability of various SSRIs and SNRIs at usual doses. There are studies on fluoxetine, sertraline, venlafaxine, citalopram, escitalopram, duloxetine, desvenlafaxine, and vortioxetine.[78–86]

Existing data do not support superior efficacy of a particular antidepressant agent or class over the others for the management of midlife depression. Still, a few important points should be taken into consideration when choosing an antidepressant for this population. First, despite small numbers and methodological limitations, data on efficacy and tolerability of various agents for this particular population could inform and guide some of the preliminary discussions with midlife women suffering from depression. Second, data on tolerability and adverse events (and how they seem to affect treatment adherence) should be carefully examined, particularly when issues such as sexual dysfunction and changes in metabolism are already part of the clinical scenario or reported as important concerns. Conversely, look for data supporting the

efficacy of some of the antidepressants for the relief of menopause-related symptoms (eg, hot flashes, pain, disrupted sleep) and QOL improvement. Finally, data available on drug safety (eg, drug-drug interactions) should always be considered because multiple medications that are often prescribed to this population.[87]

SUMMARY

Evidence-based psychotherapies, particularly behavioral-based interventions, should have a place in the treatment armamentarium to ultimately reduce the overall burden and functional impairment associated with depression in this population.[88] Nonpharmacologic or hormonal strategies (eg, exercise, balanced diet, dietary supplements) need to be better examined as additional tools to help improve QOL and reduce functional impairment during the menopause transition and beyond.

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