

## CONSENSUS RECOMMENDATIONS

# Guidelines for the evaluation and treatment of perimenopausal depression: summary and recommendations

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### Abstract

There is a new appreciation of the perimenopause – defined as the early and late menopause transition stages as well as the early postmenopause – as a window of vulnerability for the development of both depressive symptoms and major depressive episodes. However, clinical recommendations on how to identify, characterize and treat clinical depression are lacking. To address this gap, an expert panel was convened to systematically review the published literature and develop guidelines on the evaluation and management of perimenopausal depression. The areas addressed included: 1) epidemiology; 2) clinical presentation; 3) therapeutic effects of antidepressants; 4) effects of hormone therapy; and 5) efficacy of other therapies (eg, psychotherapy, exercise, and natural health products). Overall, evidence generally suggests that most midlife women who experience a major depressive episode during the perimenopause have experienced a prior episode of depression. Midlife depression presents with classic depressive symptoms commonly in combination with menopause symptoms (ie, vasomotor symptoms, sleep disturbance), and psychosocial challenges. Menopause symptoms complicate, co-occur, and overlap with the presentation of depression. Diagnosis involves identification of menopausal stage, assessment of co-occurring psychiatric and menopause symptoms, appreciation of the psychosocial factors common in midlife, differential diagnoses, and the use of validated screening instruments. Proven therapeutic options for depression (ie, antidepressants, psychotherapy) are the front-line treatments for perimenopausal depression. Although estrogen therapy is not approved to treat perimenopausal depression, there is evidence that it has antidepressant effects in perimenopausal women, particularly those with concomitant vasomotor symptoms. Data on estrogen plus progestin are sparse and inconclusive.

**Key Words:** Antidepressants – Depression – Depressive symptoms – Estrogen – menopause – Perimenopause – Psychotherapy.

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The existence of *hormone-related* mood symptoms or ‘windows of vulnerability’ for reproductive-related depression across the female lifecycle has gained attention in recent decades.<sup>1,2</sup> Epidemiologic findings, animal data and clinical observations have shed some light into plausible mechanistic hypotheses on why some but not all women may be particularly sensitive to changes in the hormonal milieu experienced premenstrually, during the postpartum period or during the menopause transition.<sup>3-9</sup> The notion of a menopause-associated depression, however, has been the focus of clinical and scientific debate for years. The lack of consensus on this issue has also led to a lack of clarity in how to evaluate and treat depression in women during the menopausal transition and postmenopausal period.

To address this gap and to provide guidelines for health care practitioners, The North American Menopause Society (NAMS) and the National Network of Depression Centers Women and Mood Disorders Task Group (NNDC) collaborated to convene an 11-member expert panel to systematically review the scientific literature on depressive disorders and depressive symptoms in perimenopausal and postmenopausal women and develop clinical guidelines. The panel addressed five topics pertaining to depressive symptoms and depressive disorders during the perimenopause, including: 1) epidemiology; 2) clinical presentation; 3) therapeutic effects of antidepressants; 4) effects of hormone therapy (HT); and 5) efficacy of other therapies (eg, psychotherapy, exercise, and natural health products). This review did not focus on the mood benefits of HT and non-hormonal treatments for vasomotor symptoms (VMS), as these are covered in NAMS position statements.<sup>10,11</sup> General guidelines for the treatment of Major Depressive Disorder (MDD) are available;<sup>12</sup> therefore, those issues are not covered here. Instead, these guidelines focus on issues relating specifically to depressive symptoms and depressive disorders in midlife women.

## METHODOLOGY

Panel members reviewed the published literature related to perimenopausal and postmenopausal women in the following areas: epidemiology of depressive symptoms and depressive disorders (JB, LR); the clinical presentation of depression (HJ, GA); the therapeutic effects of antidepressant medication on clinical depression (LC, HK); the effects of hormone therapy on depression (CS); and the effect of other therapies on depression (WB, EF). Each subgroup of experts reviewed the published literature (Medline/PubMed/PsychInfo/EMbase) for relevant clinical studies using select search terms (see each section below), then they wrote a summary of their literature review and drafted a set of clinical recommendations. These were shared with each panel member via email for feedback and each subgroup was assigned to carefully review one other topic area. The panel co-chairs (PM, SK) drafted a set of guidelines based on the literature reviews. Panel members vetted the guidelines and voted on a final set of recommendations. The preliminary guidelines were presented at the 2016 NAMS Annual Meeting and

the 2017 World Congress on Women’s Mental Health, and feedback from those presentations was incorporated into final vetting of the guidelines, including the addition of a section on Specific Populations to address issues related to depression, hysterectomy with or without oophorectomy and primary ovarian insufficiency.

The literature (English only) in each section was reviewed in a systematic manner for publications between 1980 and 2015. Each section included a search with the following terms containing the MeSH terms “depression,” “depressed,” “depressive,” “anxiety,” or “mood” in combination with the terms “perimenopause,” “menopausal transition,” “menopause,” “menopausal,” “postmenopausal,” “premenopause,” or “midlife” as well as additional terms and inclusion/exclusion criteria specific to that section. Additional search terms were used for each topic area including epidemiology (“epidemiology,” “prevalence,” or “risk”), clinical presentation (“symptoms,” “presentation,” “diagnosis,” “screening,” “scales,”), antidepressants (“antidepressant,” “SSRI,” “SNRI”), hormone therapy (estrogen therapy), “hormone therapy,” “hormone replacement therapy,” “estrogen,” “oestrogen,” and “estradiol.”) and other therapies (“psychotherapy,” “electroconvulsive therapy,” “neuromodulation,” “transcranial magnetic stimulation,” “vagus nerve stimulation,” “deep brain stimulation,” “luminotherapy,” “bright light therapy,” “sleep deprivation,” “wake therapy,” “acupuncture,” “exercise,” “Hypericum perforatum,” “St. John’s wort,” “Cimifuga racemosa,” “Black cohosh,” “S-adenosyl-L-methionine,” “S-AMe,” “phytoestrogens,” “ginseng,” “ginkgo biloba,” “folate,” “l-methylfolate,” and “omega 3 fatty acids”). Each of the three intervention sections included only those clinical trials that selectively enrolled women with clinical depression and excluded studies that examined mood benefits in non-depressed women.

The epidemiology section addressed the following three questions with systematic reviews: 1) In cross-sectional studies, what is the relationship between perimenopause stage and depressive symptoms? 2) In longitudinal studies, what is the relationship between perimenopause stage and depressive symptoms? 3) In longitudinal studies, what are the risk factors for depressive symptoms/disorder in perimenopause? Four inclusion criteria were applied: 1) community-dwelling samples, not clinical settings, 2) sample size  $\geq 200$ , with 50 or more in each menopause stage, 3) a standard depression inventory with a validated cutoff score to indicate “depressive symptoms” or the use of a structured clinical interview to indicate “diagnosed depressive disorder,” and 4) specification and application of standard criteria to determine menopause status (eg, Stages of Reproductive Aging Workshop Plus 10 [STRAW+10]<sup>13</sup> or Study of Women’s Health Across the Nation [SWAN]<sup>14</sup> criteria; specific criteria for irregularity, number of missed periods, last bleed). We use the definition of perimenopause from the STRAW+10 criteria, where perimenopause is defined as the early and late menopause transition stages as well as the early postmenopause.<sup>13</sup>

Note that this definition differs from SWAN where perimenopause includes early and late perimenopause but not the postmenopause. Also, given that the SWAN provides the longest follow-up period – 13 years of follow-up for a sample of women aged 42-52 at baseline - it is important to recognize that this body of work includes women with a maximum age of 65 and is not meant to address the topic of geriatric depression. Additionally, the following two sections were added following feedback from NAMS, 4) Is hysterectomy with and without oophorectomy a risk factor for depressive symptoms/disorders? And 5) Is Premature Ovarian Insufficiency (POI) linked to depression?

The section on the presentation of depression addressed: 1) Is there a unique or characteristic clinical presentation of depressive disorders during the menopause transition? 2) How is depression diagnosed during the menopause transition? What is the differential diagnosis of depression during the menopausal transition? 3) What symptoms commonly co-occur with depression in midlife women? 4) What are the unique psychosocial challenges associated with the menopause transition that might contribute to depressive symptoms? and, 5) What screening measures have been validated for assessing depression and depressive symptoms? Studies that were published in a peer-reviewed journal, published in the English language, and utilized a validated or standard screening scale to assess one or one or more of the following: i) menopausal symptoms, ii) psychological distress, iii) depressive disorders, iv) depressive symptoms, v) mood symptoms and vi) quality of life during menopause, were included.

The section on antidepressants addressed four questions: 1) What are the therapeutic effects of antidepressants on major depressive episodes (MDE) in perimenopausal and postmenopausal women? 2) Are there differences in efficacy between types of antidepressants in the treatment of peri- or postmenopausal women with MDD? 3) Does clinical response to antidepressants differ according to menopause status? 4) Does estrogen therapy improve antidepressant response in peri- or postmenopausal women with MDD? Only studies meeting the following criterion were included: a) use of validated instruments to measure depression (eg, Hamilton Depression Rating Scale [HDRS], Montgomery-Åsberg Depression Rating Scale [MADRS], Beck Depression Inventory [BDI], Patient Health Questionnaire-9 [PHQ-9]).

The section on hormone therapy addressed the following questions: 1) Does HT have an effect on depressive disorders in perimenopausal women? 2) Does HT have an effect on depressive disorders in postmenopausal women? and, 3) Does HT prevent depressive symptoms during the menopausal transition? The section was guided by a recent, comprehensive systematic review on the efficacy of estrogen-based interventions.<sup>15</sup> The following inclusion criteria were applied: 1) clinical administration of estrogen-based HT, and 2) assessment of mood symptoms/depression with standardized instruments. Nonintervention studies and studies using non-estrogen-based preparations or hormone-analogue agents

(selective estrogen-receptor modulators [SERMs]) were excluded from further consideration. Additionally, following feedback from NAMS, a section on hormonal contraceptives for perimenopausal women was added.

The section on other therapies on depression addressed efficacy of treatment modalities in classes that include: 1) psychotherapies, 2) somatic/physical therapies (neuromodulatory treatments, light therapy, exercise), and 3) natural products (ie, nutraceutical therapies and botanical/herbal therapies).

## EPIDEMIOLOGY OF DEPRESSIVE SYMPTOMS AND DEPRESSIVE DISORDERS IN MIDLIFE WOMEN

### In cross-sectional studies, what is the relationship between perimenopause stage and depressive symptoms?

Numerous cross-sectional studies have addressed whether perimenopausal women demonstrate a higher prevalence of or are at risk for depressive symptoms compared with premenopausal women (Table 1). Sample sizes in these cross-sectional studies ranged from 376 to 6,383 women (median, 927), and most samples included women aged between 40 and 60 years, representing six different countries, a range of ethnicities, and a range of educational attainment.

Although all studies had an adequate sample size to provide an acceptable prevalence estimate of elevated depressive symptoms in the overall sample, comparisons of elevated depressive symptoms in perimenopausal versus premenopausal women may have been underpowered in samples with a low prevalence of elevated depressive symptoms and relatively small sample sizes. The analytic approach varied, with some studies reporting adjusted results and others unadjusted. Eight of the 12 studies included found that elevated depressive symptoms were significantly more prevalent in perimenopausal versus premenopausal women, and six of these were adjusted for covariates.<sup>16-20</sup> These studies suggest that 45% to 68% of perimenopausal women report elevated depressive symptoms compared with 28% to 31% of premenopausal women.<sup>17,20</sup> In early perimenopause, 28% to 47% of women reported elevated depressive symptoms<sup>16,19</sup> and the odds of elevated depressive symptoms in this stage was higher than in the premenopausal stage. In a large cohort of ethnically diverse women, early perimenopausal women showed a 1.74-fold increased odds of elevated depressive symptoms during early perimenopause<sup>19</sup> and among Hispanic women there was a 2.45-fold increased odds.<sup>16</sup> It is difficult to conclude whether women in the late-perimenopause stage demonstrate elevated depressive symptoms because of the two cross-sectional studies that specifically included this group of women, one included only 57 women in this stage<sup>19</sup> and the other only examined depressive symptoms continuously.<sup>21</sup>

### In longitudinal studies, what is the relationship between perimenopause stage and depressive symptoms?

Prospective longitudinal studies from three U.S. cohorts addressed whether the perimenopausal stage is a period of increased risk for both depressive symptoms and depressive

**TABLE 1.** Cross-sectional studies of prevalence or odds of depressive symptoms in perimenopause compared to premenopause

Study	N	Country	Sample age range or mean/SD	Outcome measure	Percent of sample with elevated symptoms	Stage		Combined early/late
						Early peri	Late peri	
Depressive symptoms								
Chim et al. <sup>146</sup>	495	Singapore	40-60	CES-D <sup>a</sup>	6%	na	na	ns
Bromberger et al. <sup>16</sup>	3,015	US	42-52	CES-D	24%	↑ <sup>c</sup>	na	na
Juang et al. <sup>147</sup>	1,273	Taiwan	40-54	HADS-D	8%	na	na	ns
Galicchio et al. <sup>148</sup>	634	US	45-54	CES-D	25%	na	na	ns
Tangen et al. <sup>149</sup>	6,383	Norway	42-58	HADS-D	-	na	na	↑
Zainal et al. <sup>150</sup>	3,934	Malaysia	45-60	CES-D	54%	na	na	↑
Brown et al. <sup>17</sup>	639	US	45-54	CES-D	25%	na	na	↑ <sup>b</sup>
Yen et al. <sup>151</sup>	672	Taiwan	40-60	CES-D	38%	na	na	ns <sup>d</sup>
Timur et al. <sup>20</sup>	685	Turkey	40-60	BDI	29%	na	na	↑ <sup>b</sup>
Maki et al. <sup>19</sup>	1,170	US	30-65	CES-D	38%	↑	ns	na
Lin et al. <sup>18</sup>	3,359	Taiwan	40-55	TDQ	5%	na	na	↑
Maus et al. <sup>21</sup>	376	US	35-60	BDI-II	-	↑ <sup>b</sup>	↑ <sup>b</sup>	na

↑= Increased odds compared to premenopausal stage.

<sup>a</sup>CES-D 8-item scale, 7 cutoff.

<sup>b</sup>Unadjusted analysis only provided.

<sup>c</sup>Hispanics only. Association in the overall sample just missed statistical significance.

<sup>d</sup>Only significant when examined CES-D scores categorically and continuously unadjusted.

BDI, Beck Depression Inventory, 17 cutpoint; BDI-II, Beck Depression Inventory II; CES-D, Center for Epidemiological Studies Depression Scale, 20-item scale, 16 cutoff; HADS-D, Hospital Anxiety and Depression Scale, depression subscale, 8 cutoff; ns, no significant difference; na, not applicable; peri, perimenopausal; PRIME MD, Primary Care Evaluation of Mental Disorders; SD, standard deviation; TDQ, Taiwanese Depression Questionnaire, 19 cutoff; US, United States.

disorders as measured by diagnostic clinical interviews (See Table 2). These cohorts include SWAN,<sup>14,22-24</sup> the Penn Ovarian Aging Study (POAS),<sup>25-28</sup> and the Seattle Midlife Women's Health Study.<sup>29</sup> Compared with cross-sectional studies, longitudinal studies are more optimally designed to address the association between menopause transition stage and depression as well as the direction of the association. Sample sizes in longitudinal studies sizes ranged from 151 to 3,302 (median, 332), and median length of follow-up was 7 years (range, 3-15 y). Women across studies were ethnically diverse and primarily well educated. Of the 11 longitudinal studies reviewed, six (54%) suggest an increased risk of depressive symptoms during the transition,<sup>14,24,26,27,29,30</sup> with estimates of a 1.30 to 1.55 increased likelihood of depressive symptoms in the early transition and 1.71 to 2.89 increase in the late transition.<sup>14,24,27</sup> Two studies indicate that in women with no previous history of depression,<sup>26,27,30</sup> the transition poses a greater risk for elevated depressive symptoms than does remaining premenopausal, especially in those with a history of adverse life events<sup>30</sup> or vasomotor symptoms (VMS) during perimenopause.<sup>30</sup> Although the majority of studies focused on the menopausal transition, the POAS examined risk in relation to the final menstrual period (FMP). When a sizeable number of women reached postmenopause in the POAS, the risk of elevated depressive symptoms was significantly higher before the FMP with a lower risk after the FMP.<sup>25</sup> Whether women with greater racial and economic diversity show the same risk of MDD is unclear, as selection bias can affect estimates of new onset depression, particularly in studies selecting for women with no history of MDD.<sup>31</sup>

Two longitudinal studies evaluated the risk of a MDE during the menopause transition using the Primary Care

Evaluation of Mental Disorders (POAS)<sup>27</sup> or the Structured Clinical Interview for Depression (SWAN).<sup>22</sup> In adjusted analyses, the SWAN reported that women were two to four times more likely to experience a major depressive episode during the menopause transition and early postmenopause, whereas no increased risk was found during these periods in the POAS.<sup>26,27</sup> In the POAS, few women transitioned through late perimenopause and postmenopause, so there is greater confidence in findings related to the early perimenopause than later in the transition.<sup>26,27</sup> In SWAN, the women at greatest risk for MDE during the menopause transition and after were those with a history of MDD before midlife.<sup>23,32</sup> Indeed, the largest studies have not found that the risk of a MDD episode during the transition is increased when there is no prior history of MDD.<sup>23</sup> A longitudinal SWAN study compared risk factors for an MDD episode in 151 women with a history of MDD compared to 274 women without a history of MDD.<sup>23</sup> Women with a history of MDD had a higher risk of developing MDD during midlife compared with women without a history of MDD (59% vs 28%).<sup>23</sup> Additionally the risk for MDD was higher in the peri- versus premenopausal stage only for women with a history of MDD.<sup>23</sup> Overall the elevated risk for MDD in the perimenopause compared to the premenopause was primarily seen among women with a history of MDD, with inconsistent evidence of an increased risk in women without MDD prior to midlife.

### In longitudinal studies, what are the risk factors for depressive symptoms/disorders during the perimenopause?

Longitudinal studies from the United States, the Netherlands, and Australia revealed a wide range of risk factor domains for depressive symptoms and disorders

TABLE 2. Longitudinal studies of odds of depressive symptoms/disorder during the perimenopause compared to premenopause

Study	N	Length of follow-up (years)	Country	Age range or mean/SD at study entry	Outcome measure	Stage		
						Early peri	Late peri	Combined early/late
<b>Depressive symptoms</b>								
Avis et al. <sup>152</sup>	2,565	5	US	45-55	CES-D	na	na	ns
Maartens et al. <sup>153</sup>	2,103	3.5	Netherlands	51.8	EDS	na	na	ns
Freeman et al. <sup>27</sup>	332	4	US	35-47	CES-D	↑	↑	na
	152 <sup>a</sup>					↑	ns	na
Freeman et al. <sup>26</sup>	231 <sup>a</sup>	8	US	35-47	CES-D	na	na	↑
Cohen et al. <sup>30</sup>	460 <sup>a</sup>	3	US	36-45	CES-D	na	na	↑
Bromberger et al. <sup>14</sup>	3,302	7	US	42-52	CES-D	↑	↑	na
Woods et al. <sup>29</sup>	302	15	US	33-55	CES-D	ns	↑	na
Bromberger et al. <sup>24</sup>	3,296	8	US	42-52	CES-D	↑	↑	na
Morrison et al. <sup>28</sup>	436	11	US	35-47	CES-D	↓	↓	na
Freeman et al. <sup>25</sup>	203 <sup>b</sup>	14	US	42.8 ± 3.1	CES-D	na	na	↑ compared to FMP
<b>Depression Diagnosis</b>								
Freeman et al. <sup>27</sup>	332	4	US	35-47	PRIME MD	ns	ns	na
Freeman et al. <sup>26</sup>	231 <sup>a</sup>	8	US	35-47	PRIME MD	na	na	ns
Bromberger et al. <sup>32</sup>	266 <sup>a</sup>					ns	ns	ns
Bromberger et al. <sup>22</sup>	221	10	US	42-52	SCID	na	na	↑
Morrison et al. <sup>28</sup>	436	11	US	35-47	PRIME MD	ns	↓	na
Bromberger et al. <sup>23</sup>	274 <sup>a</sup>	13	US	42-52	SCID	na	na	ns
	151 <sup>c</sup>					na	na	↑

BDI-II, Beck Depression Inventory II; CES-D, Center for Epidemiological Studies Depression Scale, 20-item scale, 16 cutoff; EDS, Edinburgh Depression Scale, 12 cutoff; ns, no significant difference; na, not applicable; peri, perimenopausal; PRIME MD, Primary Care Evaluation of Mental Disorders; SCID, Structured Clinical Interview for the Diagnosis of DSM-IV Axis I Disorders; SD, standard deviation; US, United States.

<sup>a</sup>Women with no history of clinical depression at baseline.

<sup>b</sup>Compared the effect of menopausal status in a different way, using final menstrual period as the point of comparison.

<sup>c</sup>Women with a history of clinical depression at baseline; no notations indicates samples that include women with and without clinical depression.

↑ = Increased odds compared to premenopausal stage.

↓ = Decreased odds compared to premenopausal stage.

(Table 3). These include demographic characteristics (financial problems; unemployment; being black, Hispanic, or Japanese; < 50 y old; low education); somatic symptoms (VMS, bothersome symptoms, sleep problems); health related issues (prior depression, poor self-rated health, prior premenstrual complaints, severe premenstrual syndrome, use of psychotropic medications, high body mass index, history of postpartum blues, nulliparity, current antidepressant use, smoking, history of anxiety, chronic medical condition, low role functioning due to physical problems); psychosocial factors (death of partner, major stressful life event, negative attitudes toward aging and menopause, daily hassles, low social support, high trait anxiety, few close friends, tendency to ruminate); and hormones (mean and variability in follicle-stimulating hormone [FSH] and estradiol, and mean inhibin). As shown in Table 3, the evidence of an association between VMS and depressed mood is inconsistent. In SWAN there is a strong association between VMS and elevated depressive symptoms<sup>14</sup> but only a borderline significant association (p < 0.10) between frequent VMS and an MDD episode.<sup>21</sup> The POAS found the opposite pattern of results, with a significant association between VMS and MDE but not depressive symptoms.<sup>27</sup> Inconsistencies may be due to different definitions of VMS (eg, any, ≥ 6 days/2 weeks) and to the way MDD was assessed. For VMS, the association is primarily with depressive symptoms, rather than MDD. Overall, multiple and varying exposures including socioeconomic, individual psychological and social

characteristics, and health factors are associated with increased risk for depressive symptoms and MDD during the menopause transition.

### Is hysterectomy with and without oophorectomy a risk factor for depressive symptoms/disorders?

Studies examining the association between depression and hysterectomy with or without oophorectomy have yielded mixed results.<sup>33-37</sup> In an early randomized trial of ET or ET plus androgen therapy in premenopausal women, depressive symptoms worsened immediately following hysterectomy with oophorectomy, and improved significantly more with ET or ET plus androgen therapy than placebo.<sup>38</sup> A recent meta-analysis of studies published before 2012 identified 22 studies acceptable for inclusion (maximum sample size = 1,162 women; maximum follow-up = 12 years) and concluded that symptoms of depression were significantly reduced following hysterectomy.<sup>33</sup> However, the quantitative analyses combined postmenopausal women and women with oophorectomy, precluding consideration of the effects of estrogen withdrawal on depression in premenopausal women. Longitudinal studies since that time have revealed an elevated risk of depression following hysterectomy with and without ovarian conservation.<sup>34,35</sup> For example, a study of 5,336 women from the Australian Longitudinal Study on Women's Health found that the risk of elevated depressive symptoms was 20% higher in women with a hysterectomy and ovarian conservation and 44% higher in women with a hysterectomy

**TABLE 3.** Risk factors for depressive symptoms/depression in midlife women

Study	N	Length of follow-up (years)	Country	Age range or mean/SD at study entry	Outcome measure	Risk factors
Depressive symptoms						
Avis et al. <sup>152</sup>	2,565	5	US	45-55	CES-D	<b>symptoms</b> (↑ VMS, night sweats and/or menstrual problems)
Maartens et al. <sup>153</sup>	2,103	3.5	Netherlands	51.8	EDS	<b>demographic</b> (financial problems, unemployment, inability to work outside the home); <b>health</b> (prior depression); <b>psychosocial</b> (death of a partner, occurrence of a major life event)
Dennerstein et al. <sup>43</sup>	314	11	Australia	56-67	CES-D <sup>a</sup>	<b>health</b> (↑poor self-rated health, prior premenstrual complaints); <b>psychosocial</b> (↑negative attitudes toward aging and menopause, negative mood, daily hassles); <b>symptoms</b> (↑ #of bothersome symptoms)
Freeman et al. <sup>27</sup>	332	4	US	35-47	CES-D	<b>demographic</b> (Black, < 50 years of age, unemployed); <b>health</b> (hx of depressive disorders, hx of severe PMS); <b>hormonal</b> (FSH); <b>symptoms</b> (↓ sleep)
Freeman et al. <sup>154</sup>	436	5	US	35-47	CES-D	<b>health</b> (hx of PMS, hx of MDD); <b>hormonal</b> (E2 SD)
Freeman et al. <sup>26</sup>	231	8	US	35-47	CES-D	<b>hormonal</b> (E2 SD, FSH SD and mean, inhibin mean, LH)
Bromberger et al. <sup>14</sup>	3,302	7	US	42-52	CES-D	<b>demographic</b> (↓ age, financial difficulty); <b>health</b> (use of psychotropic medication); <b>psychosocial</b> (less than highly positive attitudes toward aging and menopause, ↓ social support, > 1 very stressful life event); <b>symptoms</b> (VMS)
Woods et al. <sup>29</sup>	302	15	US	33-55	CES-D	<b>demographic</b> (↓ age); <b>health</b> (↑ BMI, hx of postpartum blues, no live births, current use of antidepressants); <b>psychosocial</b> (↑ SLE)
Bromberger et al. <sup>24</sup>	3,296	8	US	42-52	CES-D	<b>demographic</b> (↓ age, ↓ education, Hispanic, Japanese); <b>health</b> (current smoker, medication for nerves or depression, ↑ BMI); <b>hormonal</b> (T); <b>psychosocial</b> (↑ upsetting life events, ↓ social support); <b>symptoms</b> (↑ VMS)
Morrison et al. <sup>28</sup>	436	11	US	35-47	CES-D	<b>demographic</b> (↓ age, black); <b>health</b> (smoker)
Freeman et al. <sup>25</sup>	203	14	US	42.8 ± 3.1	CES-D	<b>health</b> (hx of depression, current medication)
Depression Diagnosis						
Freeman et al. <sup>27</sup>	332	4	US	35-47	PRIME MD	<b>demographic</b> (Black); <b>health</b> (hx of depression, hx of severe PMS, current use of antidepressants); <b>symptoms</b> (↑ VMS, ↓ sleep)
Freeman et al. <sup>26</sup>	231	8	US	35-47	PRIME MD	<b>health</b> (↑ BMI); <b>hormonal</b> (E2 SD)
Bromberger et al. <sup>22</sup>	221	10	US	42-52	SCID	<b>health</b> (↑ BMI, hx of MDD, psychotropic medication use); <b>psychosocial</b> (↑ upsetting life event)
Morrison et al. <sup>28</sup>	436	11	US	35-47	PRIME MD	<b>demographic</b> (↓ age, Black); <b>health</b> (smoker, ↑ BMI)
Kravitz et al. <sup>155</sup>	425	12	US	46.1 ± 2.5	SCID	<b>health</b> (hx of anxiety or MDD); <b>psychosocial</b> (↑ anxiety and depressive symptoms, baseline trait anxiety, ≥2 or more upsetting life events)
Bromberger et al. <sup>23</sup>	425	13	US	42-52	SCID	<b>Among women with incident MDD: health</b> (lifetime medical condition, role physical); <b>psychosocial</b> (close friends, trait anxiety) <b>Among women with recurrent MDD: demographic</b> (↓ age); <b>health</b> (lifetime anxiety disorder, time-varying depressive symptoms); <b>psychosocial</b> (close friends, private self-consciousness/ruminative)

#= number.

<sup>a</sup>BDI-II, Beck Depression Inventory II; BMI, body mass index; CES-D, 10-item scale, 10 cutoff; CES-D, Center for Epidemiological Studies Depression Scale, 20-item scale, 16 cutoff; E2, estradiol; EDS, Edinburgh Depression Scale; FSH, follicle-stimulating hormone; hx, history; LH, luteinizing hormone; MDD, major depressive disorder; na, not applicable; ns, no significant difference; peri, perimenopausal; PMS, premenstrual syndrome; PRIME MD, Primary Care Evaluation of Mental Disorders; SCID, Structured Clinical Interview for the Diagnosis of DSM-IV Axis I Disorders; SD, standard deviation; SLE, stressful life events; T, testosterone; US, United States; VMS, vasomotor symptoms.

↑= Increased.

↓= Decreased.

without ovarian conservation compared to women without a hysterectomy.<sup>35</sup> Women on ET in that study reported higher levels of depressive symptoms than women not on ET. However, because this was not a randomized trial of ET, this association might not reflect a causal effect of ET on depression but instead might indicate that HT was prescribed to treat depressive symptoms, although their depressive symptoms persisted. A population-based study of 8,441 Taiwanese women followed for up to 10 years revealed that compared to women without a hysterectomy, those with a hysterectomy

had a 78% higher risk of elevated depressive symptoms and an 84% risk of MDD.<sup>34</sup>

### Is Premature Ovarian Insufficiency linked to depression?

Premature ovarian insufficiency or primary ovarian insufficiency (POI) is a clinical syndrome defined by loss of ovarian activity before the age of 40 and affects 1% of women.<sup>39</sup> There are few studies examining the prevalence of depression in women with POI. The lifetime prevalence of depression was found to be significantly higher in women

with spontaneous 46, XX POI (54.5%) compared with the general population (20%) and occurred as commonly before as after the onset of menstrual irregularity—a proxy for the early stages of ovarian insufficiency.<sup>40</sup> In addition to menopause symptoms, concerns about fertility and long-term health consequences are associated with reduced psychological wellbeing in women with POI.<sup>41,42</sup>

### CLINICAL PRESENTATION OF DEPRESSION

#### Is there a unique or characteristic clinical presentation of depressive disorders during the menopause transition?

Depression during midlife, presents with classic depressive symptoms, commonly in combination with menopause-specific symptoms and psychosocial challenges. The menopause transition and early postmenopausal stage are reproductive stages associated with increased risk for MDE<sup>22</sup> and are also transient windows of vulnerability for the development of subthreshold depressive symptoms.<sup>26,27,29,30,43,44</sup> The menopause transition generally spans 4 to 8 years; however, the onset of the menopause transition, compared with other reproductive transitions, is less distinct and reflects underlying hormone changes that precede the clinical markers by a variable period of time.<sup>45</sup> Difficulties in establishing the temporal association of the onset of mood changes with the menstrual markers of the menopause transition may partly explain the relative paucity of data describing unique presentations of clinical depression during and after the menopause transition.<sup>46</sup> In addition, although major strides have been made to ensure standardization, historically there has been a lack of consistency in defining depression during the menopause transition, distinguishing the severities of depression at this stage and using uniform rating tools.<sup>47</sup>

#### How is depression diagnosed during the menopause transition?

Comprehensive diagnosis of depressive disorders during midlife may involve an identification of the stage of menopause as well as clinical assessment of depressive symptoms and other psychiatric conditions. The differential diagnosis of depression during the menopause transition and after surgical menopause includes MDD, subsyndromal depression, adjustment disorder, psychological distress, bereavement, bipolar depression, and general medical causes of depression. Most women who experience a MDE during the menopause transition have had a history of MDD; therefore, the episode represents recurrence of their illness.<sup>23</sup> First lifetime onset of MDD during the menopause transition is less common.<sup>23</sup>

During the menopause transition and postmenopause, a woman may experience more losses compared with previous stages of her life. Similarly, she may also experience life stressors unique to her midlife stage (eg, caring for aging parents, sometimes while caring for children; career shifts); hence, bereavement and adjustment disorder are important to consider in the differential diagnosis.

Some women also may experience psychological distress related to awareness of aging, body changes associated with

reproductive aging, and concurrent health conditions.<sup>48</sup> Although surgical menopause may present concerns about fertility and premature aging, data surrounding surgical menopause's association with increased or decreased risk of psychological distress are largely mixed.<sup>49</sup> Psychological distress is to be differentiated from subsyndromal or minor depression.<sup>50</sup> Minor depression is characterized by exhibiting two to four symptoms of a MDE, including dysphoria or anhedonia, with associated distress and/or functional impairment.

Mood swings are also common during the menopause transition.<sup>51</sup> Previous psychiatric history, collateral, and careful delineation of symptoms may assist in differentiating mood swings commonly experienced during the menopause transition from a diagnosis of bipolar disorder. Prospective studies have demonstrated an increased likelihood of mood exacerbation (mood depression as well as elevation) in those with a history of bipolar disorder during the late menopause transition and early postmenopause.<sup>52</sup>

#### What symptoms commonly co-occur with depression in midlife women?

Several common symptoms of the menopause transition and natural or surgical postmenopause (VMS, sleep and sexual disturbances, weight/energy changes, cognitive shifts, and urinary symptoms) co-occur and overlap with the presentation of depression during this stage.<sup>53</sup> Depression itself may present with sleep, sexual, appetite, energy, and concentration difficulties. VMS and sleep disturbance are especially common and can be severe after surgical menopause.<sup>54,55</sup> An evaluation of the co-occurrence of depressive symptoms and menopausal symptoms was performed via cluster analysis in a sample of 797 women with no history of MDD who were participating in the MSFlash trials.<sup>56</sup> At baseline, there were two symptom clusters that included women with elevated depressive symptoms. In one cluster (14% of the total sample), elevated depressive symptoms were clustered with high levels of insomnia, very low sleep quality and moderately high VMS. In a smaller cluster (7% of the total sample), elevated depressive symptoms were clustered with elevated anxiety but minimally with other symptoms. In the cluster characterized by the highest level of VMS (11% of the sample), depressive symptoms were low, indicating that depressive symptoms are not uniformly present, even when VMS are severe.

Because these same symptoms also may be secondary to menopause, it becomes difficult to parse out contributing etiologies, relative contributions of each etiology, and potential additive effects.<sup>53,57</sup> In addition, symptoms unique to the menopause transition and postmenopause, including VMS and vaginal dryness, have the potential to magnify or complicate individual symptoms and global clinical experience of depressive disorders during this stage.<sup>58</sup> Furthermore, depression may affect an individual's appraisal of the degree of bother from somatic symptoms commonly encountered during the menopause transition; thereby, further magnifying the effect of symptoms on quality of life.<sup>59</sup>

### *Vasomotor symptoms and sleep*

The interrelationship between depressive symptoms, VMS, and sleep disturbances has been studied. The domino theory asserts that night sweats may be causally related to sleep disturbances that, in turn, are causally related to depressive symptoms.<sup>60</sup> Subsequent studies have supported some aspects of this theory and questioned others.<sup>61</sup> A study examining the effect of VMS on sleep via induction by a gonadotropin-releasing hormone agonist demonstrated a causal relationship between VMS and difficulty sleeping.<sup>62</sup> In the POAS cohort, where all women were premenopausal at baseline, depressive symptoms were more likely to precede VMS in the menopause transition among women who had no experience of either symptom prior to the transition, findings that challenge the causal relationships of the domino theory as a universal explanation of the association between these symptoms.<sup>63</sup> Experimental studies examining the relationship of mood with concurrent VMS and sleep disturbance have used gonadotropin-releasing hormone agonists to induce symptoms in healthy non-depressed women<sup>64</sup> and, separately, have randomized women with a MDE to estrogen therapy or placebo.<sup>65,66</sup> These studies have shown that for women without MDE, emergence of depressive symptoms on gonadotropin-releasing hormone agonists is linked with emergence of sleep disturbance, specifically sleep interruption, and with onset of nocturnal VMS, but not daytime VMS.<sup>64</sup> In contrast, among women with MDE randomized to estrogen therapy, depressive symptoms improve in concert with improvement in sleep disturbance, but not in association with VMS.<sup>66</sup> Epidemiologic studies have similarly shown that VMS are linked with risk of developing subsequent depressive symptoms,<sup>24,26,65,66</sup> but not MDE,<sup>23,26</sup> although there is a statistical trend toward an association of VMS with subsequent emergence of first lifetime onset of MDD in SWAN<sup>23</sup> and an early POAS study showed a significant association between VMS and new MDD onset.<sup>27</sup> Taken together, these experimental and epidemiologic studies provide evidence that the relationship between depressive symptoms and VMS differs between those with and without MDE, with associations observed almost exclusively among those without MDE.<sup>67</sup>

Sleep disturbance has been linked with depression in midlife women. In women with VMS, the sleep characteristics that distinguish those with versus those without a depressive disorder include prolonged sleep-onset latency, reduced perceived quality of sleep, sleep efficiency, and overall total sleep duration.<sup>61</sup> On the basis of these studies, it appears that VMS are causally related to difficulty sleeping. Difficulty sleeping, in turn, appears to be associated with depressive symptoms.<sup>64,66</sup> Symptoms characteristic of the menopause transition and early natural or surgical postmenopause may overlap and compound symptoms common to depression.

*Cognition:* Depression and menopause itself may exert effects on concentration, thereby making it difficult to disentangle individual contributions.<sup>53,57</sup> Subjective complaints of cognitive changes are common during the menopause

transition; longitudinal studies from SWAN provide some objective validation to the subjective complaints because they demonstrate a transient impairment in learning during the menopause transition.<sup>68</sup> Concurrent depressive and anxiety symptoms were associated with slower processing speed and anxiety was also associated with worse memory, but no symptom accounted for lower performance in late perimenopause compared to premenopause.<sup>69</sup> Consistent with SWAN, the POAS demonstrated a decrease in learning and memory as women transitioned through the menopause even after accounting for age, depression, anxiety and other factors that can influence cognition.<sup>70</sup> Midlife women with depression may also present with co-occurring cognitive slowing and deficits in encoding and thus have the potential of amplifying existing cognitive changes during the menopause transition.<sup>69,71</sup>

*Fatigue:* In addition, selected neurovegetative features of depression (decreased energy, increased appetite) may overlap with and compound subjective complaints of fatigue as well as weight increases commonly reported during and after the menopause transition.<sup>72</sup>

*Sexual function:* Genitourinary changes accompanying menopause may affect sexual function and desire.<sup>73</sup> Decreased libido also may be a symptom of depression.<sup>74</sup> The dual effect of depression and the menopause transition on sexual desire and performance may be additive,<sup>75</sup> an effect that may be especially true for surgical menopause.<sup>76,77</sup>

*Urinary incontinence:* There is a small and inconsistent literature suggesting a bidirectional association between urinary incontinence and depression in midlife women. Prospective cohort studies have found depressive symptoms to be a risk factor for persistent urinary incontinence.<sup>78,79</sup> Other cross-sectional studies have reported that postmenopausal women with urinary incontinence are more likely to have depressive and anxiety symptoms.<sup>80</sup> In contrast, several other studies have not observed a clear link between depression and urinary incontinence in midlife women with depression.<sup>22,23</sup> The basis for this potential association is not understood but might be related to decreased serotonin levels in the central nervous system that have been correlated with increased urinary frequency and bladder contractions.<sup>81,82</sup>

### **What are the unique psychosocial challenges associated with the menopause transition that might contribute to depressive symptoms?**

The psychosocial factors observed during the menopause transition and postmenopause may be unique to midlife. Older studies posit that depressive symptoms, previously termed “involutional melancholia,”<sup>83</sup> arose from an “empty nest” phenomenon; namely, that women may be prone to depressive symptoms when children leave the home.<sup>84</sup> This theory has since been refuted with empiric data which suggest an improvement in wellbeing in women when children leave the home and no effect of the return of adult children (“revolving door”) on mood.<sup>85</sup> Nonetheless, menopause may represent a uniquely challenging time for women. Many

women face a series of stressors including but not exclusive to caring for aging parents, death of parents, medical illness in self and family, adjusting to emotional and physical sequelae of surgical menopause and other health issues that are common to this stage of life, children leaving the home, and changes in marital status. With the onset of childbirth at an increasingly later age, women are often faced with the dual responsibility of raising young children amid caring for aging parents while navigating their careers and ensuing challenges. These multiple demands are often faced without supports in place to identify or address the ensuing distress placed on a woman during this stage.

**What screening measures have been validated for assessing depression and depressive symptoms?**

Several general validated screening measures for clinical settings, including but not exclusive to the PHQ-9, may be used for categorical determination of mood disorder diagnoses during the menopause transition as they are in other populations. In research settings, questionnaires such as the Center for Epidemiological Studies Depression Scale (CES-D), as well as the Quick Inventory of Depressive Symptomatology-Self-Report, also may be helpful in capturing symptom severity and are predictive albeit not diagnostic of MDD during midlife.<sup>86,87</sup> It is important to note that several symptoms common to the menopause transition (VMS, cognitive changes, sleep disturbances) may affect scoring.<sup>57</sup> The HDRS is also commonly used in research studies, and is clinician administered.<sup>88</sup> A menopause-specific mood disorder scale does not yet exist, but other menopause-specific validated symptom and quality-of-life (QOL) scales measuring more general parameters may be useful. The Menopause Rating Scale (MRS) incorporates a range of perimenopause measures including but not exclusive to mood, libido, and vaginal dryness.<sup>89</sup> The Menopause-Specific Quality-of-Life Scale (MENQOL) assesses and identifies psychological and somatic parameters that affect QOL during the menopause transition.<sup>90</sup> Other commonly used scales include the Greene Climacteric Scale and the Utian Quality-of-Life Scale.<sup>91,92</sup> Although these scales address domains of psychiatric symptoms, they do not distinguish distress from major depression or subsyndromal depression. Moreover, they also do not necessarily capture the duration of symptoms or the effect of mood disturbance on function.<sup>89,90</sup>

**THERAPEUTIC EFFECTS OF ANTIDEPRESSANT MEDICATIONS ON CLINICAL DEPRESSION IN PERI- AND POSTMENOPAUSAL WOMEN**

**What are the therapeutic effects of antidepressants on MDE in perimenopausal and postmenopausal women?**

Two large randomized, double-blind, placebo-controlled trials examined the efficacy of desvenlafaxine for MDD in perimenopausal and postmenopausal women defined using STRAW criteria (see Table 4).<sup>93,94</sup> Short-term treatment with 50 mg and 100-200 mg doses of desvenlafaxine led to significant improvement in depressive symptoms compared with

**TABLE 4. Large randomized trials examining the efficacy of antidepressants for major depressive disorder in well-defined perimenopausal and postmenopausal women**

Study	Design	Population	Medication	Results
Kornstein et al. 2010	Randomized double-blind, placebo-controlled 8-wk trial	387 peri- and postmenopausal women (aged 40-70 y) with MDD	Desvenlafaxine (flexible dosing 100-200 mg/d with mean daily dose 162-176 mg/d) vs placebo	Significant improvement in depressive symptoms (HAMID-17) with desvenlafaxine versus placebo; Response rate=59% vs 32%, remission rate=38% vs 22%; Effect evident as early as week 1
Soares et al. 2010	Randomized double-blind 8-wk trial with 6-month continuation phase	607 postmenopausal women (aged 40-70 y) with MDD	Desvenlafaxine 100-200 mg/d vs escitalopram 10-20 mg/d	No significant differences between desvenlafaxine and escitalopram after 8 weeks or after 6 months continuation phase
Clayton et al. 2013	Randomized double-blind, placebo-controlled 8-wk trial	434 peri- and postmenopausal women (aged 40-70 y) with MDD	Desvenlafaxine 50 mg/d vs placebo	Significant improvement in depressive symptoms (HAMID-17) with desvenlafaxine versus placebo; also significant benefits on pain and functional outcomes
Kornstein et al. 2014	Post-hoc analysis of randomized double-blind, placebo-controlled 8-wk trial	135 perimenopausal and 291 postmenopausal women (aged 40-70) with MDD	Desvenlafaxine 50 mg/d vs placebo	Significant improvement in depressive symptoms in both peri- and postmenopausal subgroups with desvenlafaxine vs placebo
Kornstein et al. 2015	Pooled data from 2 randomized, double-blind, placebo-controlled 8-wk trials	252 perimenopausal and 546 postmenopausal women (age 40-70 y) with MDD	Desvenlafaxine (100-200 mg/d) for 8 wks & Desvenlafaxine (50 mg/d) for 10 wks	Significant improvement in depressive symptoms (HAMID-17) and secondary outcomes (SDS, MRS) with desvenlafaxine vs placebo in both peri- & postmenopausal women

HAMID-17, 17-item Hamilton Depression Rating Scale; MDD, Major Depressive Disorder; MRS, Menopause Rating Scale; SDS, Sheehan Disability Scale; wks, weeks; y, years.

placebo.<sup>93,94</sup> Post-hoc analyses of pooled data from these trials showed significant improvement with desvenlafaxine in both the perimenopausal and postmenopausal subgroups, including lower symptom burden and higher remission rates.<sup>95,96</sup> To date, no other antidepressants have been studied in large randomized placebo-controlled trials of well-defined perimenopausal and postmenopausal women with MDD. There have been a number of small open-label studies of other antidepressants including selective serotonin reuptake inhibitors (SSRIs; citalopram, escitalopram, vortioxetine), serotonin-norepinephrine reuptake inhibitors (SNRIs; venlafaxine, duloxetine) and mirtazapine to treat MDD in perimenopausal and postmenopausal women that have demonstrated a positive effect on mood as well as VMS, sleep, anxiety, and pain.<sup>97-99,100-103</sup> Bupropion, a norepinephrine-dopamine reuptake inhibitor (NDRI), is sometimes prescribed alone or in combination with an SSRI/SNRI to perimenopausal women because it does not lead to as much weight gain, sexual dysfunction, or sleepiness as SSRI/SNRIs.<sup>104</sup> However, there are no RCTs of bupropion in perimenopausal women.

#### **Are there differences in efficacy between types of antidepressants in the treatment of peri- or postmenopausal women with MDD?**

A large randomized double-blind trial compared the SNRI desvenlafaxine and the SSRI escitalopram on MDD in postmenopausal women defined using STRAW criteria; no significant difference in efficacy was seen after 8 weeks of acute phase treatment nor after 6 months of continuation phase treatment (see Table 4).<sup>105</sup> These findings were in contrast to a previous analysis of a large pooled dataset by sex and age (using a cutoff of 50) comparing remission rates with venlafaxine, SSRIs, or placebo that found a significant advantage in remission rates favoring the SNRI venlafaxine over SSRIs in older women.<sup>106</sup> Another post-hoc analysis of clinical trial data using age-defined menopause status showed no difference in the efficacy of the SNRI venlafaxine versus the SSRI fluoxetine in younger or older women.<sup>107</sup> Similarly, a pooled analysis of open-label trials showed no differences in response rates to reboxetine, sertraline, or venlafaxine in older and younger women.<sup>108</sup> Some studies have noted a superior effect of an SSRI over a tricyclic or norepinephrine reuptake inhibitor (NRI) in premenopausal women, but no such differences were found in postmenopausal women in those studies.<sup>109-111</sup>

#### **Does clinical response to antidepressants differ according to menopause status?**

Several studies have examined whether there are differences in antidepressant response in premenopausal versus postmenopausal women, all using age as a proxy for menopause status. In the pooled analysis of clinical trials of venlafaxine, SSRIs, and placebo discussed above, poorer response to SSRIs was noted in postmenopausal compared with premenopausal women, whereas response to venlafaxine

did not differ by menopause status.<sup>106</sup> Another pooled analysis showed no differences in antidepressant response to either bupropion or SSRIs by menopause status,<sup>112</sup> nor did a large study of venlafaxine and fluoxetine.<sup>107</sup> Like the Thase 2005<sup>106</sup> study, several open-label studies have demonstrated relative resistance to SSRIs and other antidepressants in postmenopausal versus premenopausal women,<sup>113-115</sup> whereas others did not find a difference by menopause status.<sup>111,116-118</sup> Only one study examined menopause status as a predictor of depression recurrence during antidepressant treatment; rates of recurrence of MDD during treatment with venlafaxine or fluoxetine did not differ in pre-versus postmenopausal women.<sup>107</sup>

#### **Does estrogen therapy improve antidepressant response in peri- or postmenopausal women?**

Two post-hoc analyses of randomized placebo-controlled studies of SSRIs in older women with MDD found an interaction between use of concomitant estrogen therapy and antidepressant treatment effect, suggesting that estrogen may augment antidepressant response to SSRIs in postmenopausal depressed women.<sup>119,120</sup> Two small open-label trials showed increased or accelerated response to SSRIs in postmenopausal depressed women who also took estrogen,<sup>121,122</sup> whereas two other open-label studies showed no difference in response or remission rates in peri- or postmenopausal depressed women treated with SSRIs who were taking versus not taking estrogen.<sup>123,124</sup> In the analysis of the large pooled dataset of trials of venlafaxine, SSRIs, and placebo discussed above, concomitant use of HT in the postmenopausal women eliminated the disparity in response rates to SSRIs in pre-versus postmenopausal women; HT did not affect response rates to venlafaxine.<sup>106</sup> In a small double-blind placebo-controlled trial, estrogen augmentation improved antidepressant response in perimenopausal women with MDD in partial remission.<sup>125</sup>

### **EFFECTS OF HORMONE THERAPY ON DEPRESSION**

#### **Does HT have an effect on depressive disorders in perimenopausal women?**

At least four small studies—including two RCTs—have demonstrated the efficacy of estradiol for the management of depressive disorders (eg, MDD, dysthymia or minor depression) during perimenopause (See Table 5).<sup>65,121,126,127</sup> The two RCTs had similar designs and are considered of high quality because of the use of standardized tools to confirm the diagnosis of depression, the characterization of menopause staging using FSH levels and history of menstrual irregularity, and monitoring of treatment compliance with serum estradiol measurements.<sup>65,126</sup> Antidepressant effects were well documented (reduction in CES-D, HDRS, and MADRS scores), and significant mood improvement was observed in those experiencing new-onset or recurrent depression in the presence or absence of concomitant VMS. Moreover, the antidepressant effects of estradiol persisted after a 4-week washout

TABLE 5. Randomized trials of hormone therapy for depressed peri- and postmenopausal women

Authors	Population Studied (Type, n)	Design	Intervention	Outcome Measures	Key findings
Schmidt et al., 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., 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., 2004	Postmenopausal women with mild/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., 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., 2011	Mixed peri- 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

BDI, Beck Depression Inventory; CES-D, Center for Epidemiologic Studies-Depression Scale; DB-Double blind; EPT, estrogen-progestin therapy; E2, estradiol; ET, estrogen therapy; HDRS, Hamilton Depression Rating Scale; MADRS, Montgomery-Åsberg Depression Rating Scale; MPA, medroxyprogesterone acetate; PL, placebo; PSQI, Pittsburgh Sleep Quality Index.

period, even after re-emergence of VMS and night sweats.<sup>126</sup> There are no RCTs of combination estrogen plus progestogen for depression in perimenopausal women.

**Does hormone therapy have an effect on depressive disorders in postmenopausal women?**

Several small RCTs have examined the efficacy of HT on mood in postmenopausal women with depressive disorders and suggest that HT is not efficacious in this population. In an 8-week study, both transdermal estradiol (0.1 mg) and placebo improved depressive symptoms (HDRS scores or CES-D scores) in late postmenopausal women (N = 57; mean age=67 y; ~ 16 y after FMP) with mild-to-moderate depression.<sup>128</sup> In a 24-week trial of 129 postmenopausal women<sup>129</sup> with minor to major depressive episode (mean age =55 y) combination estradiol valerate (2 mg/d) plus dienogest (2 mg/d) significantly improved mood (HDRS) compared with placebo. However, the dropout rate was unusually high in both HT (33%) and placebo groups (58%). In an 8-week randomized, placebo-controlled trial of 72 peri- and postmenopausal women (mean age=51 y) with depression of mild to moderate severity and significant insomnia and VMS, transdermal estradiol (0.05 mg/d), zolpidem (10 mg/d), and placebo each improved depressive symptoms (MADRS scores) and there was no meaningful differences between active treatment groups and placebo. Overall improvement in mood was significantly correlated with an increase in serum estradiol over time (perimenopausal women only) and improvement in perceived sleep quality (peri- and postmenopausal women), but not to VMS or changes in objective measures of sleep.<sup>66</sup> There are insufficient data on estrogen plus progestogen for depression in postmenopausal women to guide treatment choice.

New evidence indicates that certain women are particularly vulnerable to depressed mood following estrogen withdrawal. Asymptomatic postmenopausal women (N = 56) with history of perimenopausal depression were administered transdermal estradiol (100 µg/d) in an open-label fashion for three weeks and then were randomized to receive either transdermal estradiol or placebo for 3 additional weeks in a double-blind fashion.<sup>130</sup> Although free of depressive symptoms during the open-label estradiol phase, women who were crossed over from estradiol to placebo – that is, who experienced estrogen withdrawal - reported an increase in depressive symptoms (CES-D and HDRS), whereas those who remained on estradiol therapy continued to be asymptomatic. Hot flash severity and plasma estradiol levels were similar between treatment and placebo phases.

**Does HT prevent depressive symptoms during the menopausal transition?**

To date only one randomized trial has investigated the efficacy of HT in preventing the onset of significant depressive symptoms in euthymic perimenopausal and early postmenopausal women.<sup>131</sup> A total of 172 euthymic perimenopausal or early postmenopausal women were randomly

assigned to receive either transdermal estradiol (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 elevated depression scores compared with women receiving placebo (32.3% vs 17.3%). These effects were modified by stressful life events, with greater benefits for women with stressful life events in the preceding six months, and a suggestion that women in the early perimenopausal stage may have more benefit than women in other menopause stages. Unexpectedly, VMS and history of MDD (33% of sample) did not modify the effect of HT on preventing depressive symptoms.

### **Hormonal contraceptives in perimenopausal women**

For perimenopausal women, hormonal contraceptives provide contraceptive as well as non-contraceptive benefits, including restoring regular menses, decreasing dysmenorrhea, reducing heavy menstrual bleeding, and treating VMS.<sup>132</sup> Although these benefits have the potential to improve mood, there are no published randomized trials or open-label trials of hormonal contraceptives in women with clinical depression. The Food and Drug Administration (FDA) approved a 24/4 regimen of drospirenone (3 mg) and ethinyl estradiol (0.02 mg) pill for the treatment of premenstrual dysphoric disorder (PMDD).<sup>133,134</sup> A combination pill that also includes levomefolate is also FDA approved for the treatment of PMDD. Neither formulation, however, has been studied in women with depression. Generally, for perimenopausal women, continuous oral contraceptive pills (OCPs) or cyclic OCPs with a low-dose estradiol patch during placebo week are used. During pill-free days, perimenopausal women can experience worsening of menopausal symptoms, so continuous oral contraceptive hormone use, which is effective in symptom control is generally preferred over cyclic with pill-free days.<sup>135</sup> Although it has not been studied in depression, an alternative option that is used in the perimenopause is transdermal estrogen plus a levonorgestrel intrauterine system, which provides endometrial protection and contraception and decreases VMS in perimenopausal women.<sup>136</sup>

## **EFFECT OF OTHER THERAPIES ON DEPRESSION AND DEPRESSIVE SYMPTOMS IN MIDLIFE WOMEN**

### **What nonpharmacologic therapies have at least preliminary evidence for menopause-related depressive disorders?**

*Cognitive-behavioral therapy (CBT).* CBT is a time-limited psychotherapy to help patients assess and modify distorted, depression-promoting, automatic thoughts about themselves, their current situations, and their futures. These cognitive techniques are paired with behavioral interventions to combat passive disengagement from life activities. CBT has been shown to be effective for reducing symptoms of depression, preventing depressive relapses in the general population,<sup>137</sup> and treating depressive symptoms in primary care settings.<sup>138</sup>

Practice guidelines have preferentially recommended antidepressant pharmacotherapy over psychotherapy for severe episodes of depression in general adult populations; however, recent evidence suggests that baseline depression severity may not moderate differences in antidepressant efficacy between CBT and antidepressant pharmacotherapy for adults with depression.<sup>139</sup> Combining CBT and antidepressant pharmacotherapy may be more effective for reducing depressive symptoms, improving recovery rates, and increasing adherence to treatment than medication alone.<sup>140</sup> CBT also appears to be as effective as continuing antidepressant treatment for preventing relapses.<sup>141</sup>

Two clinical trials provide initial evidence that CBT improves depression related to the menopause. In the first study, 44 women outpatients (mean age = 49 y, 52% perimenopausal, 48% premenopausal) who were not taking HT were randomly assigned to receive twice-weekly group CBT (16 sessions) or an undefined control condition.<sup>142</sup> Group CBT, but not the control condition, led to a significant improvement in depressive symptoms (BDI) from baseline. Similar results were evident in analyses of perimenopausal women only. In a second study, individual CBT (16 sessions) was delivered to 353 women (mean age = 42 y) who were not taking or were withdrawn from psychotropic medication.<sup>143</sup> Classification of menopausal stage was defined according to non-validated criteria with 169 classified as premenopausal, 76 as perimenopausal based on age range (42–51.5 y) and at least one menstrual period reported within the year before trial entry, and the remaining 108 participants as postmenopausal. Overall, 93 participants (55%) showed a positive treatment response defined as 50% or greater improvement in depressive symptoms (HDRS) from baseline, and rates did not differ by menopause status. Twenty (26%) perimenopausal and 30 (28%) postmenopausal participants achieved depressive symptom remission, defined as a HDRS total score 6 or less at study exit.

There is preliminary support that the core elements of CBT that have been shown to be efficacious in depression treatment in the general population may also apply to patients with depression related to the menopause transition. However, the lack of appropriate control conditions and lack of standardized criteria to define menopausal stage limit the data quality. Large, randomized trials of CBT specifically designed for women with depression related to menopause transition are needed. However, given the strong evidence base supporting individual or group CBT for depression in the general population, the relatively low risk of harms, and the preliminary evidence supporting these interventions in perimenopausal and postmenopausal women, CBT is a reasonable option for treatment of depression related to the menopause transition.

### **What therapies are effective for depression in general but have not been studied in the menopause?**

Several therapies are recommended for depression in general but have not been studied in the menopause. These include the psychotherapies interpersonal therapy and

mindfulness-based cognitive therapy (MBCT). Therapies recommended for treatment-resistant depression that have not been studied specifically for menopause-related depression include electroconvulsive therapy (ECT), transcranial magnetic stimulation (TMS), and vagus nerve stimulation. Similarly, light therapy for patients with seasonal affective disorder has not been studied specifically for women in the menopause transition. A Cochrane meta-analysis of clinical trials of exercise for the treatment of MDD in adults over 18 found that exercise reduces depression symptoms, but in high-quality studies, exercise confers only small benefits.<sup>144</sup> A meta-analysis of clinical trials of exercise for depressive symptoms in midlife and older women without MDD found that exercise improved depressive symptoms.<sup>145</sup>

### SUMMARY AND GUIDELINES

On the basis of the data, the expert panel makes the following recommendations for the evaluation and treatment of depression during the menopause transition.

#### Epidemiology

- The perimenopause is a window of vulnerability for the development of both depressive symptoms and major depressive episodes.
- The risk of depressive symptoms is elevated during the perimenopause even in women with no history of major depressive disorder.
- Most midlife women who experience a MDE during the perimenopause have experienced a prior episode of depression; therefore, the episode represents recurrence of their illness. First lifetime onset of MDD during this time is less common.
- Data are mixed about whether women who undergo surgical menopause are at increased or decreased risk for developing depression compared with women who transition through menopause naturally. However, recent large-scale studies show an elevated risk of depression in women following hysterectomy with and without oophorectomy. Women with primary ovarian insufficiency also have shown elevated rates of depression.
- Risk factors for depressive symptoms during the perimenopause include prior MDD, sociodemographic factors (eg, younger age, black race, financial difficulties), psychosocial factors (adverse life events, low social support), menopause symptoms (VMS, sleep disturbance), anxiety symptoms, and reproductive-related mood disturbance (eg, postpartum and/or premenstrual depressive symptoms).
- Risk factors for MDD during the perimenopause include mental health factors (prior MDD, current use of antidepressants, anxiety, trait anxiety, premenstrual depressive symptoms), sociodemographic factors (black race, high BMI, younger age), psychosocial factors (upsetting life events, social isolation), and menopausal symptoms (especially sleep disturbance).

#### Clinical presentation

- Depression during midlife presents with classic depressive symptoms, commonly in combination with menopause-

specific symptoms (ie, VMS, sleep disturbance) and psychosocial challenges.

- Several common symptoms of the perimenopause (hot flashes, night sweats, sleep and sexual disturbances, weight/energy changes, cognitive shifts) complicate, co-occur, and overlap with the presentation of depression during this stage.
- Vasomotor symptoms are associated with depressive symptoms but not MDEs, except in women with first lifetime onset of a depressive episode during the perimenopause.
- Life stressors that are common for women at midlife (eg, caring for children and parents, career and relationship shifts, aging, body changes) and personal/family illness can adversely affect mood but “empty nest” and “revolving door” have little enduring effect.

#### Assessment and diagnosis

- Evaluation includes identification of menopause stage, assessment of co-occurring and overlapping menopause and psychiatric symptoms, consideration of psychosocial risk factors, appreciation of the differential diagnosis, and use of scales to aid in disentangling symptoms and distinguishing diagnoses.
- Women with past MDEs (not necessarily hormone related) and women with severe depressive symptoms and/or suicidal ideation should always be evaluated for a mood disorder.
- The differential diagnosis of depression during the perimenopause includes MDD, subsyndromal depression, adjustment disorder, psychological distress, bereavement, depressive episodes associated with bipolar disorder, and general medical causes of depression.
- A menopause-specific mood-disorder scale does not exist; however, several general validated screening measures (eg, PHQ-9) may be used for categorical determination of mood disorder diagnoses. Validated menopause symptom and health-related quality of life scales (eg, MRS, MENQOL, Greene Climacteric Scale, Utian Quality-of-Life Scale) include mood items and may be useful in clarifying the contribution of menopause-related symptoms.

#### Treatment of MDD with antidepressants and psychotherapy

- Proven therapeutic options for depression (ie, antidepressants, CBT and other psychotherapies) should remain as front-line antidepressant treatments for MDEs during the perimenopause.
- Existing data on various SSRI and SNRI antidepressants (including citalopram, desvenlafaxine, duloxetine, escitalopram, fluoxetine, sertraline, and venlafaxine) suggest good efficacy and tolerability at usual doses. In women with a history of MDD, a prior adequate response to a particular antidepressant should guide treatment selection when MDD recurs during midlife years. Only desvenlafaxine has been studied and proven efficacious in large randomized placebo-controlled trials of well-defined peri- and postmenopausal depressed women.
- Selection of antidepressants during the perimenopause should consider the woman’s prior antidepressant trials and responses, available data on efficacy and tolerability in

this specific population, management of challenging adverse effects (eg, sexual dysfunction, weight changes) and safety (eg, drug-drug interactions), given the likelihood of concomitant use of other medications during this stage of life.

- In addition to their efficacy in treating MDD, many antidepressants (SSRIs and SNRIs) also improve menopause-related complaints (eg, VMS, pain).
- Clinicians should also consider treating co-occurring sleep disturbance and night sweats as part of treatment for menopause-related depression.

### Estrogen therapy

- There is some evidence that ET has antidepressant effects of similar magnitude to that observed with classic antidepressant agents when administered to depressed perimenopausal women with or without concomitant VMS.
- Estrogen therapy is ineffective as a treatment for depressive disorders in postmenopausal women. Such evidence suggests a possible window of opportunity for the effective use of ET for the management of depressive disorders during the perimenopause.
- There is some evidence that ET enhances mood and improves well-being in non-depressed perimenopausal women.
- Hormonal contraceptives—particularly when used continuously—have shown some benefits for mood regulation and may improve depressive symptoms in women approaching menopause.
- Transdermal estradiol with intermittent micronized progesterone may prevent the onset of depressive symptoms in euthymic perimenopausal women, but the evidence is not sufficient to recommend estrogen-based therapies for preventing depression in asymptomatic peri- or postmenopausal women and the risks and benefits must be weighed.
- Estrogen-based therapies may augment clinical response to antidepressants in midlife and older women but their use should be considered with caution – ie, preferably when also indicated for other concurrent conditions such as VMS.
- Most studies on HT for the treatment of depression examined the effects of unopposed estrogen. Data on combined HT (estrogen plus progesterone) or for different progestogens are sparse and inconclusive.
- Estrogen is not FDA approved to treat mood disturbance.

### Alternative therapies

- The available evidence is insufficient for recommending any botanical or complementary/alternative approaches for treating depression related to the perimenopause.
- It is reasonable to recommend exercise in peri- and postmenopausal women with depression, particularly when used in combination with recommended psychotherapies and pharmacotherapies.

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