Perimenopausal Depression Guidelines

Pauline M. Maki, PhD
Professor of Psychiatry and Psychology
University of Illinois at Chicago

With special thanks to

Susan Kornstein, MD
Professor of Psychiatry
Virginia Commonwealth University

Disclosure

• None
<table>
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<th>OBJECTIVES</th>
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<td>1. To explain the epidemiology and presentation of depression during the menopausal transition.</td>
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<td>2. To diagnose depression during the menopausal transition.</td>
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<td>3. To treat depression during the perimenopausal transition.</td>
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Guidelines for The Evaluation and Treatment of Depression in Perimenopausal & Postmenopausal Women

Pauline M. Maki, PhD1a; Susan G. Kornstein, MD2a; Hadine Joffe, MD MSc3; Joyce T. Bromberger, PhD4, Ellen W. Freeman, PhD5, Geena Athappilly, MD6, William V. Bobo, MD, MPH7, Leah H. Rubin, PhD8, Hristina K. Koleva, MD9, Lee S. Cohen, MD10, and Claudio N. Soares, MD, PhD, MBA11

1 Departments of Psychiatry, Department of Psychology, University of Illinois at Chicago, Chicago IL USA
2 Department of Psychiatry, Department of Obstetrics & Gynecology, and the Institute of Women’s Health, Virginia Commonwealth University, Richmond, VA USA
3 Connors Center for Women’s Health and Department of Psychiatry, Brigham and Women's Hospital and Dana Farber Cancer Institute/Harvard Medical School, Boston, MA, USA
4 Department of Epidemiology, Department of Psychiatry, University of Pittsburgh, Pittsburgh, PA, USA
5 Departments of Obstetrics & Gynecology, Department of Psychiatry, University of Pennsylvania, Philadelphia, PA
6 Edith Nourse Rogers Memorial Veterans Hospital, Bedford MA; Harvard Medical School, Boston MA USA
7 Department of Psychiatry and Psychology, Mayo Clinic, Rochester, MN, USA
8 Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, MD USA
9 University of Iowa Carver College of Medicine, Iowa City, IA USA
10 Department of Psychiatry, Massachusetts General Hospital and Harvard Medical School, Boston, MA USA
11 Department of Psychiatry, Queen’s University School of Medicine, Ontario CA

a Co-First Authors; Menopause. 2018 Oct 1; 25(10):1069-85

NAMS & NNDC convened an 11-member expert panel to:

- Systematically review scientific literature on depressive disorders in peri- and postmenopausal women
- Develop clinical guidelines

1. Epidemiology
2. Clinical presentation and diagnosis
3. Therapeutic effects of antidepressants
4. Effects of hormone therapy
5. Efficacy of other therapies (psychotherapy)
The perimenopause is a window of vulnerability for the development of both depressive symptoms and Major Depressive Episodes (MDEs).

The risk of depressive symptoms is elevated during the perimenopause even in women with no history of MDD.

Most midlife women who experience a MDE during the perimenopause have experienced a prior MDE; therefore, the episode represents recurrence of their illness. First lifetime onset of MDD during this time is less common.
Meta-analysis shows a 2-fold increased odds of depressive symptoms in the perimenopause compared to premenopause

\[
\text{Perimenopause} \quad \text{versus} \quad \text{Premenopause}
\]
\[
\text{OR} = 2.0 \\
95\% CI = 1.47-2.71, \; p < 0.001
\]


Meta-analysis shows borderline increased odds of major depression in perimenopause compared to premenopause

- The odds of major depression were not significantly increased during the perimenopause versus premenopause
  - OR=1.78 95%CI=0.99-3.2, p=0.054

Likelihood of Major Depression Increases in Peri- and Postmenopause and in Women with Vasomotor Symptoms


Major Depressive Disorder (MDD) Increases in Peri- and Postmenopausal Stages in Women with Prior MDD

SWAN: Women with no MDD hx had a lower risk of MDD during midlife than those with a prior MDD history and their risk profiles differed.

No Lifetime MDD (n = 274)
- 28% developed MDD
- Few close friends
- Medical conditions
- Perceived role limitations due to physical problems

Hx of MDD(n = 151)
- 59% developed MDE
- Younger age
- Few close friends
- Anxiety disorder
- Depressive symptoms

Bromberger et al. Risk factors for major depression during midlife among a community sample of women with and without prior major depression: are they the same or different? Psychol Med. 2015;45(8):1653-64.

FOUR DEPRESSION PROFILES OF MIDAGED WOMEN OVER 6 SURVEYS, 3 YEARS APART, FROM 1998-2013

Symptoms were higher in
- perimenopausal women
- after hysterectomy alone
- after bilateral salpingo-oophorectomy with/without hysterectomy
- hormone therapy users
- after starting or stopping hormone therapy compared with postmenopausal women

“A large number of women were excluded due to missin data, and thus the results should be interpreted with caution” 12,338 at baseline versus 5,895 women with complete data at survey 2 to 7
2. Clinical Presentation and Diagnosis

- Depression during midlife presents with classic depressive symptoms, commonly in combination with menopause-specific symptoms (i.e., VMS, sleep) and psychosocial challenges.

- Several common symptoms of the menopause transition and postmenopause (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.

Symptom clusters among MsFlash clinical trial participants

![Symptom clusters graph](image_url)
Diagnosis involves:

- identification of menopause stage
- assessment of co-occurring/overlapping menopause and psychiatric symptoms
- understanding psychosocial factors unique to midlife
- differential diagnosis for depressive symptoms
- scales to aid in disentangling symptoms & distinguishing diagnoses

Gold Standard Definitions of Menopausal Stage: STRAW+10

Harlow et al. STRAW+10 Staging Reproductive Aging Climacteric, Fertil Steril, JCEM, Menopause 2012
2. Clinical Presentation and Diagnosis

Always evaluate for mood disorder episode women who

- Have a history of multiple depressive episodes (not necessarily hormone related)
- present with severe depression and/or suicidal ideation
3. Therapeutic Effects of Antidepressants

- Proven therapeutic options for depression (i.e., antidepressants, evidence-based psychotherapies such as cognitive behavior therapy) 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.

3. Therapeutic Effects of Antidepressants

- 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.
Antidepressants are Effective in Treating Depression in the Menopausal Transition


Desvenlafaxine is Effective in Treating Depression in the Menopausal Transition

<table>
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<tr>
<th>Study</th>
<th>Design</th>
<th>Population</th>
<th>Medication</th>
<th>Results</th>
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<tr>
<td>Kornek et al 2010</td>
<td>Randomized double-blind, placebo-controlled 8-wk trial</td>
<td>387 per- and postmenopausal women (aged 40-70 y) with MDD</td>
<td>Desvenlafaxine (flexible dosing 100-200 mg/d with mean daily dose 162-176 mg/d) vs placebo</td>
<td>Significant improvement in depressive symptoms (HAM-D-17); Response rate=59% vs 32%, remission rate=38% vs 22%; Effect evident as early as wk 1</td>
</tr>
<tr>
<td>Soares et al 2010</td>
<td>Randomized double-blind 8-wk trial with 6 month continuation phase</td>
<td>607 postmenopausal women (aged 40-70 y) with MDD</td>
<td>Desvenlafaxine 100-200 mg/d vs escitalopram 10-20 mg/d</td>
<td>No significant differences between desvenlafaxine and escitalopram after 8 weeks or after 6 months continuation phase</td>
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</table>
3. Therapeutic Effects of Antidepressants

• 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.

4. Hormone Therapy

• There is some evidence that estrogen therapy (ET) has antidepressant effects in perimenopausal women with clinical depression
  • True for women with or without VMS
  • Similar in magnitude to antidepressants
• ET is ineffective as a treatment for depressive disorders in postmenopausal women.
• Suggests window of opportunity during perimenopause
Depression Improves with Estradiol Treatment in Perimenopausal but not Postmenopausal Women

<table>
<thead>
<tr>
<th>Author</th>
<th>Population</th>
<th>Design</th>
<th>Intervention</th>
<th>Outcomes</th>
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<tr>
<td>Schmidt</td>
<td>Perimenopause-related depression (n=31)</td>
<td>DB, PL Parallel</td>
<td>ET (transdermal E2), followed by MPA</td>
<td>HDRS, CES-D</td>
<td>ET improved depressive sx</td>
</tr>
<tr>
<td>Soares</td>
<td>Perimenopause-related depression (n=45)</td>
<td>DB, PL Parallel</td>
<td>ET (transdermal E2)</td>
<td>MADRS</td>
<td>ET improved depressive sx</td>
</tr>
<tr>
<td>Rudolph</td>
<td>Postmenopausal with mild/moderate depressive sx (n=129)</td>
<td>DB, PL Parallel</td>
<td>EPT (oral E2 valerate + progestin [dienogest])</td>
<td>HDRS</td>
<td>EPT improved depressive sx; high attrition rate</td>
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<tr>
<td>Morrison</td>
<td>Postmenopausal with depressive disorders (n=57)</td>
<td>DB, PL Parallel</td>
<td>ET (transdermal E2), followed by MPA</td>
<td>HDRS, CES-D</td>
<td>No significant differences</td>
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<tr>
<td>Joffe</td>
<td>Peri/postmenopausal with depressive symptoms, VMS &amp; insomnia (n=72)</td>
<td>DB, PL Parallel</td>
<td>ET (transdermal E2), Zolpidem</td>
<td>MADRS, BDI, PSQI</td>
<td>No significant differences</td>
</tr>
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</table>

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

Depression Improves with Estrogen Treatment: Randomized Clinical Trial in Perimenopausal Women

**Percent Remission**

4. Hormone Therapy

• There is some evidence that ET enhances mood and improves well-being in non-depressed perimenopausal women.

Low-Dose CEE Improves Anxiety in Women with Low VMS after Four Years of Treatment; no Effect of E2

• KEEPS: Kronos Early Estrogen Prevention Study
• 693 women (42-58 yrs; average 51.6 y)
• Early postmenopause: 1.4 years since FMP
• Randomized to 5-yr intervention with placebo or
  • Cyclic transdermal E2 (50 mg/wk) or
  • CEE (0.45 mg)
  • plus micro P (200 mg, 12 d/month)
• After 4 years of treatment, CEE (but not transdermal E2) improved anxiety and depression; effects not seen after 2 years of treatment

4. Hormone Therapy

- Estrogen-based therapies might augment clinical response to antidepressants, including SSRIs and SNRIs, in perimenopausal women with VMS.

Open-label trial shows benefits of mirtazapine for MDD in peri- and postmenopausal women on ET

N = 16 peri and postmenopausal women aged 40-61 on stable doses of ERT; Treated with mirtazapine (30–45 mg/day) for 8 weeks

4. Hormone Therapy

• 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.

4. Hormone Therapy

• Double-blind, placebo-controlled randomized trial
• 172 euthymic perimenopausal and early postmenopausal women
• Center for Epidemiological Studies–Depression Scale (CES-D), assessed at baseline and months 1, 2, 4, 6, 8, 10, and 12 after randomization
• Effects were moderated by menopausal stage – only beneficial in early menopausal transition

TE+IMP = Transdermal estradiol (0.1mg/d) plus intermittent micronized progesterone (200mg/d for 12 days every 3 months);
4. Hormone Therapy

• Most studies on HT for the treatment of depression examined the effects of unopposed estrogen.
• Estrogen-based therapies should not be considered as a strategy for prevention in nondepressed, asymptomatic peri- or postmenopausal women.
• Estrogen is not FDA approved to treat depression.

5. Other Therapies

The available evidence is insufficient for recommending the following for treating depression related to the menopause transition:

• Botanical extracts (eg, St. John’s wort, black cohosh, Gingko biloba, ginseng)
• Vitamins/Nutritional supplements (folate, omega-3 fatty acids)
• Isoflavones/Phytoestrogens
• Neuromodulatory interventions (eg, transcranial magnetic stimulation)
• Other complementary/alternative approaches (eg, acupuncture, light therapy)
OBJECTIVES

1. To explain the epidemiology and presentation of depression during the menopausal transition.
2. To diagnose depression during the menopausal transition.
3. To treat depression during the perimenopausal transition.

Thank you

- The North American Menopause Society
- The National Network of Depression Centers
- UICDR
- Panel Members