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# Depression During Perimenopause

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## Introduction

Are women more likely to develop mood disturbances as they enter menopause? It has been a long-held assumption in medical practice that this is the case. For example, over a century ago, a

woman during the climacteric was described as follows:

*“Sunshine and shadow rapidly chase each other over her daily life. She is self-sacrificing in the performance of duty at one time and, again, is*

*querulous, vacillating in purpose and capricious in temper. She is oppressed by fears of impending evils, and grows moody... There is scarcely an arrow in the armory of pain that is not unshathed at this period.”<sup>1</sup>*

The association of menopause with negative mood states is prevalent in contemporary popular literature as well, as illustrated by this passage from Pam Duncan's novel, *Moon Women*:

*"For the last six months, Ruth Ann had been having the craziest fantasies about killing people. Sometimes a family member or acquaintance came to mind, but anybody would do—mailman, Avon lady, preacher—whoever came within a thirty-foot radius during a hot flash was doomed... It was menopause. Ruth Ann knew that much. Hormones. Her periods stopped coming nearly a year ago. Cassandra said she was lucky to be getting it over with. Cassandra didn't know yet about the hot flashes, the chills, the headaches, the joint aches, the little mustache that had to be bleached a couple times a month. And she especially didn't know about the rages."*

In marked contrast to this assumption, large-scale community studies show no increase in rates of major depression in women at midlife.<sup>3</sup> Indeed, prevalence rates for major depression appear to decline in women after menopause.<sup>4</sup> In a survey of women between the ages of 26 and 80, respondents in their early fifties were more likely than women of other age groups to rate their lives as "first-rate."<sup>5</sup>

Recent research has shed light on this apparent contradiction by more carefully separating out perimenopause from postmenopause, and major depression from subsyndromal mood changes. While the vulnerability of midlife women to major depression appears to be a myth, data are accumulating suggesting that the perimenopause transition is a time of increased risk for more minor, but nevertheless potentially impairing, depressive symptoms. Although less well established, there is also some support for the hypothesis that a subset of women with histories of mood problems at other times of hormonal flux (for example, premenstrual dysphoric disorder and/or postpartum depression) has a greater propensity to develop depressive

symptoms during perimenopause.<sup>6-13</sup>

In this article, we review data linking perimenopause to depressive symptoms and identify factors influencing a woman's vulnerability to depression during the transition to menopause. We then summarize treatment interventions that can alleviate depressive symptoms during perimenopause.

### **Does Perimenopause Increase the Risk of Depression?**

The age at which women enter the transition to menopause varies; therefore, assessment of reproductive status rather than the age at which it occurs is more meaningful when investigating whether the menopausal transition causes depression. Studies using symptomatic and/or hormonal criteria to define perimenopause<sup>6,14</sup> have found that going through a natural menopause transition is not a risk factor for developing major depression, as defined by the current *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV).<sup>15</sup> By contrast, most, though not all, studies indicate that the perimenopause transition is a time of increased subsyndromal depressive symptomatology—that is, symptoms of depression that do not meet the full criteria for major depression.<sup>6,14,16-24</sup> One prospective study examining the magnitude of this heightened risk found that the 24 months surrounding the final menstrual period carry a 14-fold risk of onset of a minor depressive episode, compared with the preceding 31-year period.<sup>14</sup> Depressive symptoms that fall short of meeting diagnostic criteria for major depression may be clinically significant if they are persistent and/or cause functional impairment.<sup>25</sup>

While past episodes of depression predict subsequent depressive episodes in general,<sup>26</sup> it has been posited that a subset of women is especially vulnerable to mood changes during times of hormonal flux across their life spans.<sup>27,28</sup> Supporting this hypothesis are data demonstrating that women who have suffered from severe premenstrual syndrome (PMS) are more likely to experience depressive

symptoms during perimenopause than women without severe premenstrual depression.<sup>6-12</sup> However, a history of PMS is not a uniform characteristic of women who develop mood disturbance during perimenopause.<sup>14</sup> Fewer data exist regarding the relationship between mood disturbance during perimenopause and depression related to pregnancy or contraception. One study found that women in perimenopause who report high psychological distress were more likely to have suffered from postpartum depression or depression related to oral contraceptive use.<sup>12</sup> As with PMS, the occurrence of postpartum depression does not consistently predict depression during perimenopause.<sup>7</sup>

### **Influences on Mood**

The hormonal transition to menopause often coexists with major stresses and social role changes at midlife. A complex interplay of biological and psychosocial forces influences vulnerability to depression during this period, with each factor directly and indirectly influencing the others.<sup>29</sup> The key influences are summarized as follows:

- *Hormonal flux.* Estrogen receptors are found throughout the brain's limbic system and in parts of the hypothalamus.<sup>30</sup> Estrogen has effects on several brain neurotransmitter systems. Through effects on serotonin production and release, and by modulating serotonin receptors, estrogen acts to increase overall serotonin activity in the central nervous system. Estrogen also increases norepinephrine activity, and acts as a cholinergic agonist and as an antagonist of gamma-amino butyric acid (GABA).<sup>31</sup> While the clinical relevance of these findings is not known, the distribution of estrogen receptors in the brain and the effect of estrogen on neurotransmitter systems raises the possibility that estrogen may be important in modulating mood.

The hormonal profiles of women who become depressed during perimenopause do not differ significantly

from those of non-depressed women during perimenopause.<sup>32</sup> However, some data support the idea that at least a subset of woman is more likely to become depressed during times of hormonal flux, regardless of absolute hormone levels or direction of the change in hormone levels. For example, in a 6-week prospective, observational study of women who were depressed during perimenopause, depressive symptoms significantly improved in a subgroup of women whose plasma follicle-stimulating hormone (FSH) levels decreased by at least 50%.<sup>33</sup> Another study found that women with increasing estradiol levels reported more depressive symptoms, but women with rapidly increasing FSH levels had fewer depressive symptoms.<sup>6</sup>

The possible role of changes in androgen levels is even less well understood, but suggested by findings of lower morning dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulfate (DHEA-S) in depressed versus non-depressed women during perimenopause.<sup>32</sup>

- *The “domino effect.”* Depressive symptoms have been found to be significantly more common in women who have hot flushes and night sweats during perimenopause than in women without such vasomotor symptoms.<sup>6,11,20,34</sup> This has been posited to be due to the discomfort and sleep disturbance resulting from sweats and flushes. However, it is also possible that serotonergic abnormalities, linked with fluctuating estrogen levels, underlie both thermoregulatory problems and mood disturbances during perimenopause, especially since the vasomotor symptoms do not always precede the depressive symptoms.<sup>14</sup> Estrogen therapy can improve depressive symptoms in perimenopausal women without vasomotor symptoms,<sup>35</sup> and improved mood can persist even after estrogen is discontinued and vasomotor symptoms recur,<sup>36</sup> suggesting that this “domino effect” is not

the sole explanation for heightened vulnerability to depression during the transition to menopause.

Depressive symptoms have also been found to be significantly greater in women with sleep disturbance at midlife.<sup>37</sup> Although the direction of causality cannot be determined, alleviation of sleep disturbance, mood disturbance and vasomotor symptoms were all associated with one another in women using transdermal estradiol after hysterectomy.<sup>38</sup>

A different type of “domino effect” is the influence of general medical problems at midlife on depressed mood. General health status at midlife has been found to correlate with depressive symptoms during the transition to menopause.<sup>29</sup>

- *Psychosocial factors.* Frequent social stresses for women at midlife include caring for aging parents, parenting adolescents, occupational role changes, and loss of, or illness in, significant others.<sup>39</sup> Stressful life context has been found to correlate directly with depressed mood at midlife. Depressive symptoms during perimenopause have been found to be associated with work stress, unemployment, financial difficulty, interpersonal worries, family dysfunction, and poor social support.<sup>6,11,16,17,23,40,41</sup>

Cultural attitudes toward menopause and aging may also influence a woman’s mood during perimenopause. In some cultures, mild mood changes are expected during perimenopause, and are considered natural. Thai women, for example, refer to menopause with an idiom that means, “the blood will go—the wind will come,” referring to the changes in mood and behavior anticipated at that time.<sup>42</sup> By contrast, women in the United States appear to have more negative expectations of menopause and aging. In one survey, for example, 80% of respondents reported that women are likely to become depressed during perimenopause.<sup>43</sup>

## Does Depression Increase Risks Associated with Menopause?

While general health problems at midlife may increase the risk of depression, it also appears that the converse is true. Having depression before menopause significantly increases medical morbidity after menopause. A history of major depression may contribute to an earlier onset of menopause.<sup>44</sup> This is further compounded by cigarette smoking—the rates of which are, for unknown reasons, increased in women with major depression.<sup>45</sup> After menopause, even subsyndromal depressive symptoms predict higher rates of cardiovascular disease in women without prior histories of cardiovascular disease, and higher rates of stroke in women with prior histories of cardiovascular disease.<sup>46</sup> Women with depressive symptoms have also been found to have decreased bone mineral density.<sup>47</sup> This may be due, in part, to lifestyle factors associated with depression, such as increased cigarette smoking, decreased exercise and less optimal nutrition. It may also be due to a direct effect of elevated cortisol levels. Since depressive symptoms, and some antidepressants used to treat them, also increase the risk of falls, women with depression and osteoporosis have higher rates of fracture and resultant disability.<sup>48</sup>

Overall, the negative impact of depression on endocrine-metabolic systems, health and lifestyle is powerful enough that depression has been regarded by some as a syndrome of premature aging.<sup>49</sup> Combined with age-related changes, and changes due to estrogen depletion at menopause, untreated depression can accelerate deterioration of general well-being.

## Evaluating Depression

A key goal in evaluating a woman with depressive symptoms at midlife is to distinguish among women with mildly depressed mood in reaction to a life transition, women with subsyndromal depression that is impairing functioning, and women with major depression.

**Table 1.**  
**Interventions for Depressive Symptoms during Perimenopause**

Symptom Pattern	Primary Interventions To Consider
Mild depressed mood in response to life transitions	<ul style="list-style-type: none"> <li>• Psychoeducation/counseling</li> <li>• Lifestyle changes (diet, exercise)</li> <li>• Minimize discomfort of symptoms of perimenopause</li> <li>• Optimize general health</li> <li>• Improve social support</li> </ul>
Subsyndromal depression that impairs functioning	<ul style="list-style-type: none"> <li>• Interpersonal or cognitive-behavioral psychotherapy</li> <li>• Estrogen therapy* (if there is another indication, such as hot flashes)</li> </ul>
Major depression	<ul style="list-style-type: none"> <li>• Antidepressant medication</li> <li>• Psychotherapy</li> <li>• Adjunctive estrogen therapy* (for partial responders to antidepressants)</li> </ul>

\*Estrogen is not approved by the FDA as a treatment for depression. As in other clinical situations, a progestogen should be prescribed along with estrogen in women with intact uteri to protect against an increased risk of endometrial cancer.

By definition, a major depressive episode includes depressed mood and/or loss of interest or pleasure most of the day, nearly every day, for at least 2 weeks, along with at least four of the following symptoms: appetite changes, sleep problems, psychomotor agitation or retardation, diminished energy, feelings of worthlessness or guilt, diminished concentration, and thoughts of death. Subsyndromal depressive episodes include some of these symptoms, but not enough to meet the full criteria for major depression. This distinction helps determine which women are most likely to need antidepressant medication and/or formal psychotherapy, as contrasted with women likely to respond to education, counseling and lifestyle changes (Table 1).

### Interventions

Optimal treatment of depression during perimenopause is often multifaceted, reflecting the various factors that contribute to depression during this biocultural transition period. For most women, useful interventions include counseling about normative midlife experiences, optimizing general health

and reducing discomfort from the physical symptoms of perimenopause. Women whose depressive symptoms are adversely affecting social or occupational functioning may additionally benefit from formal psychotherapy. Women with moderate to severe major depression, or depression that is not responding well to other measures, may benefit from antidepressant medication.

*Psychotherapy.* For many women, perimenopause coincides with midlife social role transitions.<sup>50</sup> Illness in themselves and others and the death of loved ones may lead to a heightened awareness of mortality. As children grow and spouses find their own ways of managing midlife, many women are also adjusting to changes in family roles and relationships. Concomitantly, some women are also experiencing role changes at work. Sometimes, these constitute promotions to positions of influence befitting a midlife woman's experience and maturity, but in jobs in which youth is valued, midlife women may become less appreciated and more vulnerable.

Because social role transitions have a prominent influence on depression at midlife for many women, interpersonal

psychotherapy (IPT) can be particularly effective.<sup>51</sup> IPT is time-limited psychotherapy that focuses on navigating role transitions successfully. As adapted to midlife, IPT focuses on identifying lost roles, new roles and altered roles, and a woman's satisfactions and dissatisfactions with each. Through techniques including brainstorming, role-play and rehearsal, IPT helps a woman relinquish outdated, ill-fitting roles, and to reconnect with her personal attributes that were unduly suppressed by those roles. Therapy then focuses on helping the woman to renegotiate roles and relationships, such that they are a better fit with her needs and wishes.

For women with cognitive styles and behavior patterns that fuel depressed mood, cognitive-behavior therapy (CBT) can be highly effective. CBT identifies and reframes tacit "basic assumptions" that powerfully influence depressed mood. An example of a depressive "basic assumption" is a negative overgeneralization, such as a widow believing that no one will ever love her again because she is old and therefore unlovable. CBT also targets and modifies depressive behaviors, such as social isolation.

*Antidepressant medication.* Some women with major depressive episodes can respond well to psychotherapy as a sole treatment modality, particularly when there is a clear link between discrete life stresses, poor coping skills, and depressive symptoms. However, most women with major depressive episodes respond best to a combination of antidepressant medication and psychotherapy, and many will respond well to medication alone. Key principles of choosing an optimal antidepressant medication for a woman going through perimenopause are as follows:

- Choose a medication that is most likely to be effective. Since decreased serotonergic neurotransmission is implicated in depression during perimenopause, and since there are some data to support greater efficacy of serotonergic antidepressants in women,<sup>52</sup> selective serotonin reuptake

inhibitors (SSRIs) are the most widely used antidepressants. However, some women who do not respond well to SSRIs have greater therapeutic response to serotonin-noradrenergic reuptake inhibitors (SNRIs), which are more balanced in their effects on major neurotransmitter systems.

- For women with vasomotor symptoms, consider an antidepressant that has demonstrated effectiveness in alleviating hot flashes, such as fluoxetine, paroxetine, or venlafaxine.<sup>53-55</sup> Be aware, however, that some women experience vasomotor symptoms as a side effect of antidepressants.<sup>56</sup> Also note that while fluoxetine, paroxetine, and venlafaxine are FDA-approved for the treatment of depression, they are not FDA-approved for treating hot flashes.
- Choose agents that will not adversely affect comorbid medical conditions and that may even alleviate those medical conditions. For example, highly sedating antidepressants such as trazodone or mirtazapine, or antidepressants causing orthostatic hypotension, such as tricyclics, may increase the risk of falls and fractures in women with osteoporosis. The SNRIs venlafaxine and duloxetine can elevate blood pressure. Antidepressants that raise serum glucose levels, such as some tricyclics, could worsen diabetes mellitus. By contrast, duloxetine can alleviate diabetic peripheral neuropathic pain and might be a helpful choice for women with comorbid depression and diabetes.
- For women using other medications, choose an antidepressant less likely to have adverse drug-drug interactions. Although each drug combination requires individual scrutiny, citalopram and escitalopram tend to have fewer drug-drug interactions than other antidepressants.

*Hormone therapy.* As a sole agent, estrogen is not effective for treating major depression during or after menopause, and is not approved by the FDA for this

indication. However, some studies have found that estrogen can alleviate subsyndromal depressive symptoms during perimenopause, but not after menopause.<sup>36,57-59</sup> One of these studies<sup>36</sup> included a post-treatment washout period. During the washout, improved mood was sustained even though somatic symptoms, including hot flashes, returned, suggesting that estrogen's antidepressant effects were not solely due to relief from somatic symptoms associated with perimenopause.

Since estrogen is a key modulator of serotonin, it has been suggested that estrogen replacement therapy might augment serotonergic antidepressants during or after perimenopause. Supporting this hypothesis are studies demonstrating that brain serotonin receptors in ovariectomized rats did not down-regulate as expected in response to antidepressants until the rats were given estradiol.<sup>60</sup> However, estrogen replacement therapy given in naturalistic fashion (based on what study participants' physicians felt was clinically indicated rather than on specific study protocol) has not been demonstrated to effectively augment fluoxetine in women.<sup>61,62</sup> Augmentation studies that more specifically identify groups of women whose moods change during times of hormonal flux are currently under way.

The potential benefits of estrogen for alleviating depressive symptoms occurring during perimenopause must be weighed against the risks of estrogen use, including short-term side effects such as bleeding and breast tenderness. In addition, women with intact uteri need a progestogen added to estrogen to protect against a heightened risk of endometrial cancer. There are conflicting data about whether adding a progestogen worsens mood and/or counters the beneficial effects of estrogen on mood. Studies examining the mood effects of progestogens specifically during perimenopause have generally not found that they promote depression. For example, adding micronized progesterone to the treatment regimens of women in

perimenopause whose depressive symptoms had remitted with either estradiol or combined estradiol and citalopram had no effect on mood.<sup>59</sup> Another study<sup>57</sup> similarly found no attenuation of estrogen's therapeutic effect on most mood symptoms when medroxyprogesterone acetate was added. In that study, one symptom (early morning awakening) did worsen somewhat once the progestogen was added. Each of these studies had small numbers of study participants, and only added a progestogen for a short (1- to 2-week) period of time, so the findings are inconclusive. By contrast, several studies of women in menopause (rather than in perimenopause) have noted adverse effects on mood in at least a subset of women receiving a progestogen along with estrogen.<sup>63-66</sup>

Scientists are envisioning a time when genetic markers will identify which women will respond best to antidepressants, which to estrogen, and which to a combination of both.<sup>67</sup> Data thus far suggest that depressive symptoms during perimenopause are not a primary indication for hormone therapy. If a woman with subsyndromal depressive symptoms needs hormone therapy for vasomotor symptoms, it may be reasonable to see whether the hormonal intervention will simultaneously treat the depressive symptoms before implementing other antidepressant measures. Likewise, if a woman with depressive symptoms during perimenopause has a partial response to antidepressant medication, and other measures (such as psychotherapy and exercise) are not effective, a short course of estrogen therapy can be attempted to see whether this boosts the efficacy of the antidepressant. If adjunctive estrogen is effective in a woman with an intact uterus, a progestogen should be added, and effect on mood monitored. If mood worsens, switching to a different progestogen may help, although there are no data yet available demonstrating differential effects on mood for different progestogens. Intermittent progestogen use has been attempted in some cases, but there are no systematic data yet

**Table 2.**  
**Exercise Counseling at Midlife**

Define overall goals	<ul style="list-style-type: none"><li>• Relief from depressive symptoms</li><li>• Prevention of onset or recurrence of depressive symptoms and other health problems</li><li>• Weight loss</li><li>• Personal growth</li><li>• Competition</li><li>• Enjoyment</li><li>• Socialization</li></ul>
Define strengths and weaknesses in three key areas	<ul style="list-style-type: none"><li>• Aerobics</li><li>• Strength</li><li>• Flexibility</li></ul>
Identify ways to incorporate exercise into lifestyle	<ul style="list-style-type: none"><li>• Cumulative exercise is as beneficial as sustained exercise (for example, 10-minute walks three times in a day versus a 30-minute workout)</li><li>• Broaden range and type of exercise</li><li>• Include partner and/or friends</li></ul>

available demonstrating that this confers adequate protection against endometrial cancer.

**Herbal remedies.** Despite widespread use of herbal remedies to alleviate mood changes,<sup>68</sup> there is little systematic evidence of their efficacy. To date, there are no data supporting the efficacy of herbal products for treating major depression at perimenopause. Some preliminary data support the efficacy of kava and black cohosh root extract for alleviating anxiety during perimenopause.<sup>69</sup> The data are more convincing for kava, but the risks of kava—including the potential for hepatotoxicity—limit its usefulness.

**Exercise.** Aerobic exercise demonstrably alleviates depressed mood, decreases vasomotor symptoms, and enhances quality of life during perimenopause and beyond.<sup>70,71</sup> National Institutes of Health (NIH) guidelines recommend at least 30 minutes of moderate-intensity exercise on most days. Recommended exercise intensity achieves 60%–90% of maximum heart rate (defined as 220 minus age). However, a survey of women ages 50–64 revealed that less than half of the participants reported any regular recreational exercise, and less than 25% met NIH guidelines.<sup>72</sup>

Direct counseling by physicians regarding exercise can have a significant impact on how much women exercise. One study, for example, found that patients whose physicians advised them to exercise were 50%–60% more likely to do so.<sup>73</sup> Counseling is most effective when it is patient-specific and individually tailored to a woman's goals and capabilities. Table 2 summarizes guidelines<sup>74</sup> for counseling women about incorporating exercise into a comprehensive treatment plan for preventing and alleviating perimenopausal depression.

### Summary and Conclusions

Due to a combination of hormonal flux and social role changes, the transition to menopause (perimenopause) is a time of increased risk of depressive symptoms. Even subsyndromal depression, if undetected and not addressed, can impair social and occupational functioning and can increase medical morbidity after menopause.

Perimenopausal depressive symptoms can be treated effectively with a multifaceted approach, combining lifestyle changes with interpersonal or cognitive-behavioral psychotherapy and/or antidepressant medication if indicated.

In a subset of women, estrogen therapy may be an effective adjunct to antidepressant medication.

Perimenopause, as the threshold of a new phase of life, is a time of risk and opportunity. Identifying and treating depression at this key transition time can make the difference between a slide into frailty, disability and early demise and a renewed sense of purpose, authenticity and strength as a woman enters menopause ■

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