Depressive symptoms in perimenopause

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Depressive symptoms are common in perimenopause. Women who may be more at risk include those with a family history or personal history of depression or a history of adverse mood changes in relation to fluctuating hormones such as occur in premenstrual syndrome or premenstrual dysphoric disorder. First-line treatments are either selective serotonin reuptake inhibitors or serotonin-norepinephrine reuptake inhibitors, but menopausal hormonal therapy may be another option.

KEY WORDS: depression, perimenopause, menopause, SSRI, SNRI, hormone therapy

Womens Healthcare. 2022;10(5):28-32. doi: 10.51256/WHC102228

Although vasomotor symptoms (VMS) are recognizable as a bothersome aspect of menopause, negative mood symptoms also are common. The fluctuating levels of estrogen and progesterone during perimenopause may put some women at risk, and their symptoms can manifest differently when compared to premenopausal women. Mood changes can have a negative impact on a woman's quality of life, but the research is limited because of the difficulty in defining both perimenopause and depression, as well as inconsistencies among rating tools.[1,2] This article reviews the influence of both estrogen and progesterone on mood, identifies factors that may place perimenopausal women at risk for depressive symptoms, and discusses assessment and the pharmacologic treatment options of selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), and/or menopausal hormone therapy (MHT). Nurse practitioners providing care for perimenopausal women have an opportunity to improve the menopause transition experience through attention to negative mood changes.

Estrogen and progesterone's impact on the brain

Estrogen receptors are located throughout regions of the brain that regulate mood, sleep, and cognition.[3,4] Estrogen has a favorable influence on mood by increasing the amount of both serotonin and noradrenaline.[4] It accomplishes this by limiting the activity of monoamine oxidases and increasing tryptophan hydroxylase to expand serotonin synthesis and increase its availability in the synaptic cleft for transmission.[4] Further, estrogen increases noradrenaline synthesis by decreasing monoamine oxidases and increasing tyrosine hydroxylase.[3] It also influences dopamine to syn-

thesize more noradrenaline.[4] Finally, estrogen stimulates brain-derived neurotropic factor and therefore may be neuroprotective.[5]

Less is known about progesterone's role in mood when compared to estrogen. However, similar to estrogen, progesterone has receptors throughout the brain and regulates gene expression, modulation of neurotransmitter systems, and activation of signaling cascades.[6] Progesterone and allopregnanolone, one of progesterone's metabolites, are involved in neuroprotective mechanisms, cognitive function, and mood.[6] Decreased levels of allopregnanolone have been associated with depression in women.[5] It is unclear if the variance in allopregnanolone levels influences mood or if it is an individual's reaction to the variation that affects mood.[7] Little is known about progesterone's other metabolites and/or synthetic progesterone.[6]

Perimenopause and mood changes

Perimenopause is the time period leading up to menopause and on average lasts 4 years.[8] The onset of perimenopause begins with irregular menstrual cycles or other menopause-related symptoms and concludes with 12 consecutive months of amenorrhea.[9] As women age, the hypothalamic-pituitary-ovarian axis becomes less sensitive to estrogen, ovulation no longer occurs on a regular basis, the follicular phase is shortened, and at times the luteal phase estradiol is elevated in comparison to that in premenopausal women. Due to these changes, women spend longer times in the luteal phase and are vulnerable to premenstrual symptoms.[9] Later in the perimenopausal transition, folliculogenesis no longer occurs, both estradiol and progesterone levels drop, and women remain amenorrheic.[9]

Some women may have an unfavorable response to the fluctuating levels of hormones that predispose them to depressive symptoms.[10] A longitudinal study of 438 women spanning 20 years reported that the risk of depression was higher in perimenopausal women and early menopausal women.[11] Perimenopausal depression may manifest differently when compared to depression in premenopausal women.[10] For example, in the perimenopause, sadness and irritability may be more labile, with women reporting overall lower levels of depression but higher levels of anger, hostility, sleep disturbance, and fatigue.[10] A study of 50 mildly depressed perimenopausal women found irritability to be a unique symptom, separate from depression, and related to estradiol variability.[12] Not only are the presenting symptoms of depressive mood different in perimenopausal women but also there is likely to be overlap with bothersome symptoms of menopause such as fatigue, difficulty sleeping, or a decrease in sex drive.[9]

Risk factors for depression during perimenopause

The "window of vulnerability" refers to a woman's increased risk of depression during perimenopause and how well her brain can adapt to the fluctuating levels of estrogen and progesterone during the menopause transition.[4] Risk factors for maladaptation include a prior history of major depressive disorder (MDD), which is the strongest predictor for a reoccurrence during perimenopause, and a history of hormone-related mood symptoms such as premenstrual syndrome (PMS) or premenstrual dysphoric disorder (PMDD), which are moderately linked.[13] Both of those groups of women may have a genetic predisposition and vulnerability to hormonal fluctuations. An expert panel of members from the North American Menopause Society (NAMS) and the Women and Mood Disorders Task Force of the National Network of Depression Centers reviewed the literature of depressive symptoms and depressive disorders in perimenopausal women.[14] The panel concluded that depressive symptoms were more prevalent in perimenopausal women when compared to premenopausal women, especially in women with a previous history of MDD (59% vs 28% in women without a history).[15] The Study of Women's Health Across the Nation Mental Health Study (SWAN MHS) also reported that both a personal and family history of depression or anxiety increased a woman's risk of developing depression in late perimenopause or menopause.[15]

Apart from a personal or family history of depression, bothersome physical symptoms of perimenopause and menopause may be associated with depressive symptoms. A systematic review of the association between vasomotor symptoms and depression found a statistically significant positive association in 9 of 17 studies, but the reviewers included the caveat of moderate-to-high risk of bias.[16] Decreased estrogen levels can cause genital and urinary adverse changes in at least 50% of menopausal women.[8] A retrospective cohort, matched study demonstrated that women with vulvovaginal atrophy (VVA) compared to women who did not have VVA had increased rates of anxiety, depression, and MDD most notably in those age 45 to 54 years.[17]

Finally, a study demonstrated that women with two or more adverse childhood events (ACE) (eg, abuse, neglect, other trauma) had an increased risk of lifetime MDD and in-

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cident menopause MDD compared to women with zero ACEs.[18] Furthermore, when two or more ACEs occurred after puberty, there was an increased risk of incident menopause MDD, but no lifetime MDD when compared to women with zero ACEs.[18] The authors hypothesized that altered neurochemistry and behavior developed when adverse events occurred during a time of fluctuating estradiol.[18] Similarly, the subsequent hormonal fluctuations of perimenopause increased the risk of MDD.[18]

In addition to biologic risk factors, there are health-related and psychosocial risk factors for depression in perimenopause and menopause. These may include but are not limited to physical inactivity, sleep disturbances, chronic pain, physical limitations, single status, low income, low education, and minority status.[19] Perimenopausal women also may have unique additional stressors such as taking care of both aging parents and dependent children, changes in marital status, and/or mid-life health issues.[9]

Screening and assessment

Drawing hormone levels in perimenopausal women with complaints of mood changes is not advised. Research on estrogen levels and corresponding symptoms in perimenopausal women is limited. Because of the variability of the hormones, daily sampling during a woman's cycle would be ideal, but perhaps not feasible, and that information could not be broadly applied to all women.[20] Furthermore, it may be the individual's reaction to the variable hormones and not a specific value.[20]

The best way to screen for depressive symptoms is to ask all perimenopausal women and to be mindful that those with a personal or family history of depression and/or a history of PMS or PMDD are especially vulnerable. In addition, the nurse practitioner should inquire about stressors that are common to midlife women including their perception of menopause. Unfortunately, there is not a perimenopause or menopause specific screening tool for depressive symptoms. One option for screening is the PHQ-9, a self-administered screening tool for depression.[9] However, common bothersome symptoms of menopause such as difficulty sleeping or concentrating can skew results. An example of a more menopause specific screening tool is the Utian Quality of Life (UQOL), a self-administered screening tool to assess menopause QOL issues, including emotional QOL.[9] However, it also has limitations in that it does not distinguish between major depression and depressive symptoms.[9]

Treatment options

Cognitive–behavioral therapy

Cognitive–behavioral therapy (CBT) is effective for treating depression in the general population in both individual and group settings.[14] Although there is not research specific to its efficacy in managing depressive symptoms in perimenopausal women, because of its benefits otherwise and low risk it is still recommended.[14] The goal of CBT is to help women recognize and change thoughts they may have that facilitate depression along with behavioral interventions.[14] These positive effects have been shown to be persistent for a year or more after therapy ends.[21]

Selective serotonin reuptake inhibitors/serotonin-norepinephrine reuptake inhibitors

At any reproductive stage, including perimenopause, first-line therapy for MDD are antidepressants and behavioral-based psychotherapy.[22] Selective serotonin reuptake inhibitors increase the concentration of synaptic serotonin. Serotonin-norepinephrine reuptake inhibitors increase serotonin, norepinephrine, and dopamine by blocking proteins and stopping their reuptake. The EMAS [European Menopause and Andropause Society] position statement recommendation for management of depressive symptoms in perimenopausal and menopausal women is to start with an SSRI, but if there is an inadequate response within a month, switch

to an SNRI.[21] However, both SSRIs and SNRIs have proven efficacy and tolerability at the usual doses.[21] If an individual with a history of depression previously had a positive response to a particular antidepressant, that medication should be prescribed.[21] Thus far, only desvenlafaxine, an SNRI, has been studied and shown to be effective and well tolerated in perimenopausal and menopausal women in large randomized placebo-controlled trials.[23]

In addition to treatment of mood disorders, SSRIs and SNRIs have additional potential benefits for perimenopausal women. These are prescribed off label for the treatment of vasomotor symptoms and are not to be confused with paroxetine salt 7.5 mg, the only US Food and Drug Administration-approved nonhormonal medication for the treatment of VMS and not for depression or anxiety. SSRIs and SNRIs also may help with sleep, an attractive benefit for perimenopausal women who may be struggling with sleep difficulties. A meta-analysis of seven articles reviewed the safety and effectiveness of antidepressants for sleep disturbances in perimenopausal and menopausal women.[24] The authors concluded that serotonergic antidepressants were effective for sleep in women regardless of a diagnosis of MDD or presence of VMS.[24]

Menopausal hormone therapy

Due to the correlation between estrogen and progesterone and mood regulation, MHT may be another option for treatment of depression in perimenopausal women. Per the NAMS 2022 position statement, in women who are within 10 years of menopause and/or younger than age 60 years, the benefits of MHT are likely to outweigh the risks.[25] The position statement notes that the approved FDA indications are for VMS, prevention of bone loss, premature hypoestrogenism, and genitourinary symptoms.[25] However, it states there is some evidence that estrogen therapy may have antidepressant effects in perimenopausal women but not postmenopausal women.[25] Furthermore, estrogen therapy may improve mood and augment clinical response to antidepressants.[25]

There is some research to support the efficacy of MHT for the treatment of depressive symptoms. In one study, the researchers concluded that women with a history of MDD have different mood and neural responses that have not adapted to the lower estrogen in perimenopause and menopause and may benefit from estradiol administration.[26] Conversely, women without a history of MDD were successful in adapting their brain activity and may have a negative response to stress from the addition of estradiol.[26]

Furthermore, estrogen has been effective in improving mood even when adjusted for treating bothersome perimenopausal symptoms. A study concluded that estradiol and progesterone was helpful in preventing depression independent of treating VMS in the early menopause transition.[27] The researchers contributed this positive response due to decreasing the estradiol variability and withdrawal.[27] Another study compared the effects of estradiol, raloxifene, and a phytoestrogen in perimenopausal women with depression.[28] Neither raloxifene nor rimostil (an extract of isoflavones from red clover) improved mood or cognition, and while estradiol also did not improve cognition, it did improve mood even when adjusted for improving sleep.[28]

In combined MHT, progesterone is prescribed as an antiestrogen to prevent uterine hyperplasia.[9] However, if there is a contraindication to estrogen, only progesterone may be prescribed. A systematic review of seven randomized controlled trials looked at the use of progesterone for the treatment of menopausal bothersome symptoms including mood changes.[29] Of these, only four studies examined the treatment of mood changes with progesterone and none found it effective.[29] The authors added the caveat that the largest study excluded women with a mood score over 10 on the Greene Climacteric Scale and that participants included those 0 to 20 years from the time of menopause.[29]

Finally, perimenopausal women who do not want to become pregnant need contraception until menopause. Hormonal contraception can be helpful in managing abnormal uterine bleeding and treating VMS. However, although there are FDA-approved combined oral contraceptives for PMDD, there are no published randomized trials or open-label trials of hormonal contraception in the treatment of women with depression.[9]

Conclusion

When choosing a treatment option for depressive symptoms or a reoccurrence of MDD, an SSRI or SNRI can be considered as first-line treatment. If the patient has had a previous positive response to a specific antidepressant it can be the initial choice. Furthermore, if a patient is also having VMS, SSRI and SNRIs can be effective, but if there is concern about AE with an SSRI or SNRI, such as weight gain or sexual dysfunction, consider MHT. MHT is the gold standard for treatment of VMS, but there is evidence that it is also effective for depressive symptoms. With either treatment, follow up with the patient in 4 weeks to discuss efficacy and AE. If at that time, she has had some

improvement, but continues to have depressive symptoms, prescribe an SSRI/SNRI with MHT. Estrogen has a synergistic relationship with serotonin, and studies have shown an even greater response with both.

In conclusion, although research is limited on perimenopausal depressive symptoms and no validated screening tool for assessment exists, nurse practitioners can still effectively provide assessment and treatment. In that context, it is important to provide a safe and supportive space, exemplify an open and attentive posture, and listen to women. ■

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