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Depression During the Menopausal Transition: An Update on Epidemiology and Biological Treatments

Abstract: The menopausal transition is often marked by physical symptoms (e.g., vasomotor and sexual) and is sometimes accompanied by emotional changes that follow the decline in ovarian functioning. Although the absolute majority of women experience a smooth transition into postmenopausal years, this period in a woman's life has been associated, in some cases, with higher risk to develop depressive symptoms. Recent evidence supports the notion that the transition may also constitute a "window of vulnerability" for some women to develop new-onset or recurrent depression. Serotonergic and noradrenergic antidepressants as well as transdermal estradiol have been shown to be effective in alleviating depressive and vasomotor symptoms in symptomatic, midlife women. In this review, the authors discuss the epidemiology of depression during the menopausal transition and update the current biological treatment strategies used to manage this condition in midlife women.

Women are at higher risk to develop a major depressive disorder (MDD) than men during their lifetime. Whereas the risk in women during the reproductive life is 1.7 times higher, no significant differences have been observed during childhood (1) or among elderly women, who are in their late postmenopausal years (2), suggesting a possible link between higher risk for depression in women and reproductive years.

Menopause is defined as the final menstrual period as a consequence of loss of ovarian function. However, menopause is not a sudden and isolated episode in woman's life. It is a biological event that starts many years before the final menstrual period (3). The period of transition from reproductive life to menopause also represents a time in life when significant psychosocial challenges may occur, along with emotional changes and the emergence of physical symptoms associated with the progressive decline of ovarian function (3–5). Cross-sectional studies that assessed psychological distress or depression in women during the menopausal transition revealed mixed results, mostly due to methodological differences. Two large community-based studies found higher scores for psychological distress and depressive symptoms in postmenopausal compared with premenopausal women (6, 7). However, in another community sample of 304 women, no association between depression and the menopausal transition was noted with the use of the Women's Health Questionnaire and the Profile of Mood States scales (8). Using the Hospital Anxiety and Depression Scale, Juang et al. (9) found that anxiety and depression were significantly associated with the presence of hot flashes in both peri- and

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postmenopausal women in a sample of 1,273 women between the ages of 40 and 54.

Unlike cross-sectional studies, most prospective studies have consistently suggested that the menopausal transition is a period of heightened risk for the development of depressive symptoms and/or MDD. Most prospective studies used the Center for Epidemiologic Studies Depression Scale to assess depressive symptoms in women across the menopausal transition (10). The Penn Ovarian Aging Study followed 436 women for an average of 4 years and found that the severity of depressive symptoms was higher during the transition to menopause and decreased after menopause (11). The Massachusetts Women's Health Study investigated 2,356 middle-age women for 5 years and showed an increased risk for depression in perimenopausal women, especially among those with menopause-related vasomotor symptoms (12). The Study of Women's Health Across the Nation followed 3,302 women, and the Seattle Midlife Women's Health Study followed 508 women. Both studies revealed a heightened risk for depression during the perimenopausal period and early postmenopausal years (up to 2 years postmenopause), with the presence of hot flashes being an independent risk factor (13–15). Other factors have been identified as being associated with depression during the menopausal transition, including age, ethnicity (higher risk in African American and lower risk in Asian populations), low education, family history of depression, postpartum blues or depression, high body mass index, use of hormone therapy or antidepressants, history of premenstrual dysphoric disorder, cigarette smoking, stressful life events, and presence of vasomotor symptoms (11–17), reinforcing the complex, multifaceted aspect of depression during this period in women's life.

The risk for new-onset depression during the menopausal transition has been investigated by two long-term prospective studies that enrolled and followed midlife women with no previous history of depression. The Harvard Study of Moods and Cycles studied 460 women with no previous history of MDD for 6–8 years. In this study, women who entered perimenopause were nearly twice as likely to develop significant depressive symptoms than those who remained premenopausal (18). The Penn Ovarian Aging Study followed 231 women who also had no previous history of depression for 8 years. Perimenopausal women were 4 times more likely to have depressive symptoms and twice as likely to meet the criteria for MDD as premenopausal women. Interestingly, greater variation in estradiol and follicle-stimulating hormone levels was associated with both higher depressive scores and diagnosis of MDD (19).

In sum, long-term, community-based longitudinal studies have provided strong evidence that the menopausal transition is a period of higher risk for depression for some women. Although multiple risk factors (psychosocial, life stressors, and comorbid medical conditions) appear to independently modulate such risk, the presence of vasomotor symptoms and hormonal fluctuation seems to be closely associated with depressive symptoms during the menopausal transition. Thus, it is likely that treatment strategies to improve menopause-related symptoms may also reduce the risk of emotional disturbance in this population.

EVIDENCE-BASED TREATMENT STRATEGIES

ANTIDEPRESSANTS

Several open trials have provided evidence that selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs) are efficacious for the treatment of MDD (20, 21) and vasomotor symptoms (22–24) in perimenopausal and/or postmenopausal women. Open trials using monotherapy with citalopram and escitalopram presented high remission rates of depressive symptoms (86.6% and 75%, respectively). In addition to the improvement in depressive symptoms, there was also a significant improvement in menopause-related symptoms, e.g., hot flashes, night sweats, and somatic complaints (21, 25). Mirtazapine and citalopram were tested as adjunctive treatments to estrogen therapy in depressed peri/postmenopausal women, with remission rates of 87.5% with mirtazapine and 91.6% with citalopram (21, 26). Thase et al. (27) reanalyzed a pooled data set of eight randomized controlled trials to determine the efficacy and possible sex-age interactions of antidepressants in patients with MDD. This study showed higher remission rates with the SNRI venlafaxine (48%) than those with SSRIs (28%) among depressed women aged >50 years who were not receiving estrogen therapies. The difference between the two treatment groups, however, was significantly reduced among depressed women receiving estrogen-based therapies. These results might indicate that reproductive aged women may have benefit from the priming/synergistic effects of estrogens while receiving SSRIs. Conversely, it is possible that in the context of very low levels of circulating estrogen during the postmenopausal years, women would not sustain the same response to SSRIs and could have a more robust response to antidepressants that act preferably on noradrenergic neu-

rotransmission. A recent study comparing a SSRI (escitalopram) and a SNRI (desvenlafaxine) for the treatment of MDD in postmenopausal women, however, revealed no significant differences between the treatment groups with respect to efficacy and tolerability (28). The SNRI duloxetine showed remission rates of 78.6% in the treatment of depression in postmenopausal women after 8 weeks. Importantly, duloxetine also showed a positive effect in the amelioration of menopause-related symptoms (20).

HORMONE THERAPY

The initial findings of the Women's Health Initiative (WHI), published in 2002, were focused on the use of estrogen plus progestin in healthy postmenopausal women as a preventative strategy for cardiovascular diseases. These initial findings, published in 2002, raised concerns regarding the long-term safety of hormone therapy (HT) in postmenopausal women (29), and the study was interrupted before its completion. Consequently, many health professionals and their patients became more cautious or reluctant to initiate HT or to continue to use HT for longer periods of time. In light of these initial concerns, the U.S. Food and Drug Administration (FDA) requested, in 2003, that all labels on estrogen and estrogen-progestin replacement therapy should be revised to carry a boxed warning stating the increased risks for heart disease, heart attacks, strokes, and breast cancer. The warning also urged that physicians should prescribe the lowest doses of estrogens and estrogen-progestin products and for the shortest duration to achieve treatment goals. Despite subsequent, revised analyses of the WHI findings and the growing body of evidence regarding the efficacy and safety of distinct HT preparations when properly tailored to a patient's needs, the FDA warning has not been revisited to date.

Interestingly, in Ontario, Canada, the interruption of the WHI study was followed by a sharp decrease in prescriptions of HT that occurred in parallel with a marked increase in prescriptions of antidepressants to women 40 years of age or older (30). Some have postulated that such a change in prescription patterns was suggestive of the development of depressive and/or anxiety states in some women after abrupt HT interruption and/or a switch in patients and doctors' preference toward nonhormonal strategies to manage menopause-related symptoms.

A few randomized placebo-controlled trials have investigated the antidepressant effects of estrogen during the menopausal transition. Transdermal 17β-estradiol (50–100 μg) was used in two clinical trials (6- to-12-week trials) for the treatment of MDD, minor depression, or dysthymia in perimenopausal women, with remission rates of 68%–80% compared with 20%–22% with placebo (31, 32). These findings were not consistent with a subsequent study with transdermal estradiol (100 μg for 8 weeks), which did not show efficacy of this hormone intervention for the treatment of depression in postmenopausal women (33). Thus, the menopausal transition might not only be a critical window of risk for depression but also a window of opportunity to consider hormonal strategies as part of the armamentarium for the management of depression, particularly in the presence of other menopause-related complaints (34).

BOTANICAL AGENTS

To date, no studies have investigated the efficacy of botanical agents in the treatment of peri/postmenopausal women with MDD. Nonetheless, one randomized controlled trial that investigated 301 women with climacteric complaints but no diagnosis of MDD showed a 41.8% improvement in depressive symptoms as measured by a decrease in Hamilton Depression Rating Scale scores from baseline (18.9 ± 2.2) to 16 weeks (11.0 ± 3.8) with a combination of black cohosh and St. John's wort (*Hypericum perforatum*) (35). These results are consistent with those from a 12-week open trial with St. John's wort in 111 women (aged between 43 and 65 years old) with climacteric symptoms, in which participants without depression showed significant improvement of psychological and somatic symptoms (36).

OTHER AGENTS

In the search for new treatment options for depression during the menopausal transition, we have recently investigated the effectiveness of quetiapine XR. Using a placebo lead-in phase followed by an 8-week open trial, we found that quetiapine (range 150–300 mg/day) was efficacious in the treatment of depression and alleviation of menopause-related symptoms in peri/postmenopausal women (37).

SUMMARY

In sum, available evidence indicates that transdermal estrogen, SSRIs, and SNRIs are effective in the treatment of MDD during the menopausal transition. However, antidepressants remain the first choice for the management of depression in any given age/reproductive staging group. More

systematic data on botanical agents and other nonhormonal treatment strategies for depression in peri/postmenopausal women are needed to evaluate the benefits of these agents. Women with a lifetime history of depression who are unable or unwilling to use hormone therapies may benefit from the effects of nonhormonal and nonpharmacological strategies (such as exercise, acupuncture, and cognitive behavior interventions) for menopause-related symptoms. It is worth stressing that the presence of vasomotor symptoms and other menopause-related complaints appears to be associated with a higher risk for the new onset or reemergence of depression during the menopausal transition (13, 14).

QUESTIONS AND CONTROVERSIES

The underlying biological mechanisms that might lead some women to develop a higher risk for recurrent and new onset of depression during the menopausal transition remain unknown. Previous studies reporting that hormone fluctuations, rather than absolute hormonal levels, are more likely to be associated with the onset of depressive symptoms during certain female reproductive life events (14, 38) support the current hypothesis that the transition to menopause represents a "window of vulnerability" for depression (34, 39). This notion of windows of vulnerability is based on the fact that sex differences in the prevalence of mood disorders seem to emerge after puberty and decline during the postmenopausal years. A closer look at women's moods during the reproductive years reveals that approximately 20%–40% of women report moderate to severe premenstrual symptoms (physical and emotional—the latter including irritability and premenstrual dysphoria) and that 10%–12% of postpartum women meet the criteria for postpartum depression (39, 40). These two "windows of risk" corroborate the notion that some women are particularly sensitive to development of mood symptoms when facing *normal* variations in the hormonal milieu.

Estrogen receptors are widely distributed throughout the brain (41, 42). Furthermore, the effects of estrogen have been observed in the hypothalamus, prefrontal cortex, hippocampus, and brain stem, cerebral regions known to be closely associated with mood and cognitive regulation (42). The "cross-talk" between estrogen and mood appears to be quite complex and modulated at least in part by the effects of estrogen on monoaminergic neurotransmitters, especially serotonin and norepinephrine (43). Estrogen regulates serotonin neuronal firing, increases serotonin and norepinephrine synthesis, and modulates the availability and gene expression of serotonin and norepinephrine receptors (40, 41).

Joffe et al. (44) have recently shown that the interactions between sleep, vasomotor symptoms, and depression can be more multifaceted than initially thought. By using objective and subjective sleep parameters in perimenopausal and postmenopausal women with and without depression, they showed that depressed women spent less time in bed and had shorter total sleep time, longer sleep-onset latency, and a tendency toward lower sleep efficiency than did nondepressed women. Nonetheless, measurements of sleep interruption (wake time after sleep onset, number of awakenings, and duration of awakenings) did not differ between depressed patients and nondepressed control subjects. Interestingly, when vasomotor symptoms (e.g., hot flashes and night sweats) were taken into consideration, depressed women reported poorer perceived sleep quality than nondepressed women with vasomotor symptoms. Moreover, no increased frequency of nocturnal vasomotor symptoms, more awakenings, or more time spent awake after sleep onset were observed among depressed women. This study does not support, therefore, the hypothesis that the development of depression in menopausal women is due to the sleep disruption caused by vasomotor symptoms (the domino hypothesis). Moreover, a recent population-based cohort study showed that hot flashes and depressive symptoms occur early in the menopausal transition and that depressive symptoms are more likely to *precede* vasomotor symptoms in women who report both symptoms (17).

The presence of vasomotor symptoms is thought to be related to the dysregulation of the thermoregulatory center in the hypothalamus, which is controlled in part by fluctuations in estrogen levels and noradrenergic tone (45). Taken together, these data suggest that women's brains are constantly challenged to adapt to hormonal variations, which could render some women more vulnerable to development of mood symptoms during times of chaotic or unpredictable hormone fluctuations such as the menopausal transition.

RECOMMENDATIONS

The hypothesis that the menopausal transition may constitute a window of vulnerability for the development of MDD in midlife women has gained more attention in recent years. Little is known, however, about the exact mechanisms that contribute to the occurrence of this phenomenon. More tailored treatment strategies to address the

spectrum of physical and psychological complaints at this stage in life are lacking. In the post-WHI era, it is imperative that health professionals become aware of the impact of menopause (natural or surgical) on psychological well-being, particularly when managing symptomatic women who are unable or unwilling to use hormone therapies. Larger studies testing the efficacy of nonhormonal options (i.e., selective estrogen receptor modulators, herbal supplements, and psychotropic agents) are strongly encouraged to expand treatment strategies available for this population.

Moreover, physicians and health professionals should be encouraged to incorporate questions regarding reproductive status and past reproductive-related psychiatric events into their medical/psychiatric history. Antidepressants remain the treatment of choice for the management of depression during the midlife years. Nonetheless, the use of hormonal strategies, particularly estrogen-based therapies, has been shown not only to improve depressive symptoms but also to promote alleviation of menopause-related complaints (e.g., vasomotor symptoms, sexual dysfunction, and sleep disruption) and improvement in overall functioning and quality of life. As pointed out by most gynecological, endocrine, and menopause societies, hormone therapies should still be carefully considered as part of the treatment armamentarium available for symptomatic midlife women.

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