Challenges and Opportunities to Manage Depression During the Menopausal Transition and Beyond

Claudio N. Soares, MD, PhD, FRCPC[a,b,c,*], Benicio N. Frey, MD, PhD[a,c]

KEYWORDS

• Menopause • Depression • Anxiety • Vasomotor symptoms
• Perimenopause • Estrogen

Women are at higher risk than men of developing depression and such risk is particularly high during the reproductive years.[1] Although the risk for developing a major depressive disorder (MDD) among women during their lifetime is 1.7 times higher than that observed in men, no significant differences have been observed in the childhood years[2] or among the elderly, when women are predominantly postmenopausal.[3] Similarly, anxiety disorders have been reported to be more prevalent in women compared with men.[4] Given that gender differences in mood and anxiety disorders seem to emerge after puberty and decline during the postmenopausal years, it has

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[a] Department of Psychiatry and Behavioural Neurosciences, McMaster University, ON, Canada
[b] Department of Obstetrics and Gynecology, McMaster University, ON, Canada
[c] Mood Disorders Division, Women's Health Concerns Clinic, St Joseph's Healthcare, 301 James Street South, Suite F614, FB 638, Hamilton, ON L8P 3B6, Canada
* Corresponding author. Mood Disorders Division, Women's Health Concerns Clinic, St Joseph's Healthcare, 301 James Street South, Suite F614, FB 638, Hamilton, ON L8P 3B6, Canada.
E-mail address: csoares@mcmaster.ca

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been postulated that the fluctuation of gonadal hormones might exert a modulatory effect on women's vulnerability to these disturbances. A closer look at women's mood during the reproductive years reveals that about 20% to 40% of women report moderate to severe premenstrual symptoms (PMS) and that 10% to 12% of postpartum women meet criteria for postpartum depression (PPD); these 2 windows of risk corroborate the notion that some women are particularly sensitive to developing mood symptoms when facing normal changes in the hormonal milieu.

Estrogen receptors are widely distributed throughout the brain[5,6] and the effects of estrogen have been observed in the hypothalamus, prefrontal cortex, hippocampus and brain stem, and cerebral regions known to be closely associated with mood and cognitive regulation.[6] Much of the interaction between estrogen and mood is believed to be associated with the effects of estrogen on monoaminergic neurotransmitters, especially serotonin and norepinephrine.[7] Estrogen regulates serotonin neuronal firing, increases serotonin and norepinephrine synthesis, and modulates the availability and gene expression of serotonin and norepinephrine receptors.[5,8]

More recently, the modulatory effect of estrogen on serotonin and noradrenaline neurotransmission has been linked to the development of depressive symptoms. Studies in vivo and in vitro have provided good evidence that there is a close reciprocal relationship between estrogen and serotonin transmission. For instance, studies revealed selective estrogen-induced changes in serotonin transmission, binding, and metabolism in cerebral regions such as the amygdala. Studies on estrogen add-back in ovariectomized animals show that the administration of estrogen affects serotonin neurons and its afferent and target neurons. Moreover, it has been shown that estrogens selectively increased serotonin receptor density in brain regions containing estrogen receptors, such as the hypothalamus, the preoptic area, and the amygdala. The noradrenergic system is also under the influence of estrogen. It has been observed that estrogen increases noradrenaline availability and synthesis while reducing its turnover. It has recently been shown that, compared with young reproductive women, postmenopausal women not on hormone therapy have a blunted serotonin response measured by either the serotonin agonist metachlorophenylpiperazine or abnormal prolactin responses to the specific serotonin-releasing and reuptake inhibiting agent, *d*-fenfluramine. Estrogen therapy had a positive effect on serotonin tone because both acute and long-term estrogen therapy were associated with increased serotonin responsivity. The results from animal models revealed that estrogen enhances neurogenesis, synaptic plasticity, dendritic spine density, and connectivity in hippocampal formation, suggesting that estrogen may have neuroprotective effects and may modulate neuronal plasticity. In addition, the ability of estrogen to act as a neutrophic factor may be associated with the activation of a brain-derived neurotrophic factor (BDNF) signaling system. BDNF levels seem to be higher with higher estrogen levels during the menstrual cycle and while using hormone therapy following menopause. These results corroborate the neurotrophin hypothesis of depression, which is based on the effect of recurrent stress and a putative antidepressant effect associated with the BDNF cascade; however, this hypothesis has never been investigated in the context of menopausal transition.

The presence of vasomotor symptoms (VMS, namely hot flashes and night sweats), believed to be related to the dysregulation of the thermoregulatory center, seem to be associated with fluctuations in estrogen levels and increased noradrenergic tone in the hypothalamus.[9] Curiously, selective serotonin reuptake inhibitors (SSRIs) and selective serotonin and norepinephrine reuptake inhibitors (SNRIs) are efficacious for the management of depression and VMS. These data suggest that the brain in women is constantly challenged to adapt to hormonal variations, which could render some

women vulnerable to developing mood and anxiety symptoms during times of chaotic or unpredictable hormone fluctuations such as the menopausal transition.

The transition to menopause is typically characterized by a complex set of emotional and physical symptoms associated with the progressive decline of ovarian function.[10] Population studies have demonstrated that vasomotor symptoms, sleep disturbances, and vaginal dryness are particularly prevalent in peri- and postmenopausal compared with premenopausal women.[11] Several community-based prospective studies have clearly shown that menopause transition is a period of heightened risk for recurrent and new-onset depression (as discussed in detail later), which is in line with current hypothesis suggesting that the transition to menopause represents a window of vulnerability for depression.[12,13] Moreover, accumulated evidence shows that hormonal and nonhormonal interventions are useful for the management of affective disorders in perimenopausal women.[14,15] In this article, some of the most relevant studies that have investigated the emergence of depressive and anxiety states during the menopausal transition are highlighted and available evidence-based strategies in the treatment of anxiety and depression in this population are presented.

COMMUNITY-BASED EPIDEMIOLOGIC STUDIES

Data from community-based cross-sectional studies that assessed psychological distress or depression in women during menopausal transition revealed mixed results.[16–18] Bromberger and colleagues (2001)[17] found higher scores of psychological distress in early perimenopausal women compared with pre- and postmenopausal women in a large multiethnic study of women aged 40 to 55 years across the United States (N = 10,374). In another study of 1434 women between 45 and 55 years of age depressive symptoms were found to be significantly higher in postmenopausal compared with premenopausal women.[16] Slaven and Lee,[19] on the other hand, reported no association between depression and menopausal transition in a community sample of 304 women from Australia who were assessed with the Women's Health Questionnaire and the Profile of Mood States scales. Juang and colleagues[18] examined a sample of 1273 women between the ages of 40 and 54 years using the Hospital Anxiety and Depression Scale and demonstrated that anxiety and depression were significantly associated with the presence of hot flashes in peri- and postmenopausal women. Several other studies reported anxiety (traits and state) as being significantly correlated with the severity of sleep disturbance in women during the menopause transition.[20–22] No such association was found in premenopausal women,[20] suggesting that perhaps the effect of anxiety on sleep disturbance may be caused by the higher incidence of hot flashes and night sweats in this period.

Joffe and colleagues[23] have recently shown that the interactions between sleep, vasomotor symptoms, and depression can be more complex than initially believed. By using objective and subjective sleep parameters in perimenopausal and postmenopausal women with and without depression, they demonstrated 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 compared with women who were not depressed; however, measurements of sleep interruption (wake time after sleep onset, number of awakenings, duration of awakenings) did not differ between depressed and nondepressed participants. When vasomotor symptoms were taken into consideration, depressed women with VMS reported poorer perceived sleep quality than nondepressed women with VMS. The association between depression and worse sleep was seen despite a similar frequency of nocturnal VMS in the 2 groups. No increased frequency of nocturnal VMS, more awakenings, or more time

spent awake after sleep onset were observed among depressed women; therefore, the domino hypothesis that explains the development of depression in menopausal women as a result of the sleep disruption caused by VMS was not supported.

Other factors that have been associated with anxiety and depressive symptoms during the menopause transition are: history of stressful live events, history of PMS and/or mood disorders, poor social support, lower education, age, and living in a rural region.[16,18,24,25] Some but not all cross-sectional studies suggest that the menopausal transition may be associated with a higher risk for developing depression and anxiety. However, cross-sectional studies are not suitable for the investigation of temporal changes in mood and anxiety during the menopausal transition and early postmenopausal years.

Unlike the cross-sectional studies, most prospective studies[26–30] confirmed the transition to menopause as a period of heightened risk for development of depressive symptoms and/or depression, perhaps with the exception of Kaufert and colleagues.[31] The Penn Ovarian Aging Study followed 436 women from the community across the menopausal transition for an average of 4 years[28]; in this study, the severity of depressive symptoms, as measured by the Center for Epidemiologic Studies Depression Scale (CES-D) was higher during the transition to menopause and decreased after menopause; this increased risk remained significant after controlling for past history of depression, age, PMS, poor sleep, hot flashes, race, and employment status.[28] The investigators proposed that depressive and menopause-related symptoms may be mechanistically related, given that a history of severe PMS and the presence of hot flashes and sleep disturbance were independent predictors of depressive symptoms and diagnosed MDD. The Massachusetts Women's Health Study was a community-based study that investigated 2356 middle-age women for 5 years using the CES-D scale for the assessment of depressive symptoms in the transition to menopause.[26] Perimenopausal women exhibited an increased risk for depression and such risk was even higher among those with menopause-related vasomotor symptoms. Two other independent community-based studies evaluated large samples of middle-age women: the Study of Women's Health Across the Nation (SWAN; N = 3302)[27] and the Seattle Midlife Women's Health Study (N = 508).[30] Both studies also revealed a heightened risk for depression during the perimenopausal period, with the presence of hot flashes being an independent risk factor.

To assess whether the transition to menopause increases the risk for new-onset depression, 2 long-term prospective studies followed women with no history of depression across the menopause transition.[32,33] In the Harvard Study of Moods and Cycles, 460 never-depressed women were followed up for 6 to 8 years and those who entered the perimenopause were nearly twice as likely (odds ratio [OR]=1.8 [1.0–3.2]) to develop significant depressive symptoms compared with those who remained premenopausal. In this study, the presence of vasomotor symptoms and history of significant life events were independent predictors of higher risk for depression.[32] In the Penn Ovarian Aging Study, 231 women with no history of depression were followed for 8 years; perimenopausal women were 4 times more likely to have high CES-D scores and twice as likely to meet criteria for MDD than premenopausal women.[33] In addition, greater variation of estradiol and follicle-stimulating hormone levels (calculated from the standard deviation of hormonal levels) was associated with higher depressive scores and diagnosis of MDD; this particular finding is indicative that fluctuations of hormonal levels, rather than their absolute levels, may play a significant role as a trigger for depressive symptoms in biologically vulnerable women. This result is consistent with 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.[30,34] Several other factors have also been associated with depression during menopausal transition, including age, ethnicity (higher risk in African American, lower risk in Asian population), education, family history of depression, postpartum blues or depression, body mass index, use of hormone therapy or antidepressants, cigarette smoking, and stressful life events[26–30] reinforcing the complex, multifaceted aspect of depression.

Rocca and colleagues[35] examined a cohort of women who underwent oophorectomy before the onset of menopause (average follow-up was 25 years) and an aged-matched sample from the same community who had not undergone the same surgical procedure. In this study, those who underwent surgery (bilateral oophorectomy, N = 666) had a significant increased risk for developing depressive symptoms (hazard ration [HR] = 1.54, 95% confidence interval [CI] = 1.04–2.26) and anxiety symptoms (HR = 2.29, 5% CI = 1.33–3.95) compared with the referent group (N = 673). These results remained significant after adjusting for age, education, and type of surgery; moreover, the risks were even greater among those who underwent surgery at younger age.[35] The investigators speculated that these findings could be associated with the early loss of putative neuroprotective effects of estrogen levels throughout the reproductive life, and with the deficiency of testosterone and progesterone after surgery, resulting in an adverse effect on the hypothalamus-pituitary-gonadal axis; putative genetic variants could also increase the risk for these outcomes (ovarian disorders and psychiatric disturbances) independently.

Longitudinal studies looking specifically at the risk for anxiety in perimenopausal women indicated that natural (ie, nonsurgical) transition to menopause is associated with increased risk for anxiety, after controlling for the presence or severity of depression. Freeman and colleagues (2005)[36] followed up 436 midlife women for 6 years and found that hot flashes were strongly associated with anxiety, especially in women who were in the early menopausal transition. There was a dose-response effect between the severity of anxiety and the presence of hot flashes, with women with high anxiety scores being 4 times more likely to report hot flashes compared with women with no anxiety; those with moderate anxiety scores had a 3-fold increased risk for hot flashes. Anxiety remained strongly associated with hot flashes after controlling for depression, age, race, menopause stage, body mass index, smoking, and estradiol levels. More recently, the same group investigated the relationship between menopausal stage and anxiety, depression, mood swings, headache, and concentration difficulties in the same cohort after 9 years of follow-up.[37] Anxiety achieved its peak during early menopausal transition and returned to premenopausal levels in the postmenopausal years. In addition, women with a history of premenstrual syndrome were twice as likely to report anxiety compared with those with no history of premenstrual syndrome. In the SWAN study, the association between vasomotor symptoms and several health and lifestyle factors was examined in 3198 midlife women during a 6-year follow-up.[38] This study suggested a mutual relationship between anxiety and vasomotor symptoms; at baseline, women reporting more vasomotor symptoms were more likely to be anxious than women with fewer vasomotor symptoms (53.6% vs 19.1%; $P<.0001$). Conversely, more baseline anxiety was an independent factor for more vasomotor symptoms at the end of the 6-year follow-up (OR = 3.10; CI = 2.33–4.12).[38] Long-term, community-based longitudinal studies provide strong evidence that the menopausal transition is a period of higher risk for depression and anxiety. Although multiple risk factors seem to independently modulate such risk, the presence of vasomotor symptoms and hormonal fluctuation seem to be closely associated with emotional disturbance. Thus, it is likely that treatment strategies to ameliorate

menopause-related symptoms can not only improve women's quality of life but may also decrease the likelihood of emotional disturbance in this population at risk.

TREATMENT STRATEGIES

Treatment strategies specifically targeting the management of depression and anxiety during menopausal transition are scarce. The few randomized placebo-controlled trials (RCTs) conducted to date have primarily focused on the efficacy of hormone therapies in depressed women. Although several open trials have suggested that SSRIs and SNRIs can be effective in the treatment of depression in perimenopausal women, large RCTs are lacking. In addition, most treatment studies assessed anxiety symptoms as secondary outcomes or included populations with low anxiety levels. Nevertheless, as further discussed, available evidence suggests that hormonal and nonhormonal agents are useful tools for the management of depression and anxiety in perimenopausal women.

DEPRESSION

The few RCTs that investigated the antidepressant effects of estrogen found that estradiol can be efficacious for the treatment of depressive disorders. Transdermal 17β-estradiol, 50 to 100 μg, has been used in clinical trials (6–12-week trials) for the treatment of major depression, minor depression, or dysthymia in perimenopausal women, with remission rates of 68% to 80% compared with 20% to 22% with placebo.[14,15] Transdermal estradiol 100 μg for 8 weeks was not effective in the treatment of depression in postmenopausal women,[39] suggesting that the menopausal transition might not only be a critical window of risk for depression but also a window of opportunity for the use of hormonal strategies in the management of depression.[12]

The initial findings from the Women's Health Initiative (WHI) had a significant negative effect on physicians' and patients' perception of the long-term safety and benefits of hormone replacement therapies (HRT)[40]; as a result, many health professional and their patients became more cautious or reluctant to initiate HRT or to stay on HRT for longer periods of time; others started seeking nonhormonal strategies to improve menopause-related physical and psychological discomforts.[41,42] In Ontario, Canada, for example, right after the interruption of the WHI study, a sharp decrease in prescriptions of HRT occurred in parallel with a marked increase in prescriptions of antidepressants to women 40 years of age or older[43]; such change in prescription patterns was suggestive of the development of depressive and/or anxiety states in some women following abrupt HRT interruption and/or a switch in patients and doctors' preference toward nonhormonal strategies to manage menopause-related symptoms.

Several open trials have provided evidence that SSRIs and SNRIs are efficacious for the management of depression[44,45] and vasomotor symptoms[46–48] in perimenopausal and/or postmenopausal women. Remission rates of depressive symptoms were considerably high after monotherapy with citalopram and escitalopram (86.6% and 75%, respectively).[45,49] In addition to the alleviation of depression, there was a significant improvement in menopause-related symptoms (eg, hot flashes, night sweats, and somatic complaints). Mirtazapine and citalopram were tested as adjunctive treatments to estrogen therapy in depressed peri- and postmenopausal women, with remission rates of 87.5% with mirtazapine and 91.6% with citalopram.[45,50]

More recently, a pooled analysis of 8 RCT studies showed higher remission rates with the SNRI venlafaxine (48%) compared with SSRIs (28%) among depressed women more than 50 years of age who were not receiving estrogen therapies; the difference between the 2 treatment groups, however, was significantly reduced

among depressed women receiving estrogen-based therapies.[51] These results led many to speculate that reproductive-aging women might benefit from the priming/synergistic effects of estrogens while on SSRIs. Conversely, during times of unstable estrogen levels (ie, perimenopause) or in the absence of menopause-related estrogen therapies during postmenopausal years, some women would not sustain the same response to SSRIs and could have a more robust response to antidepressants that act preferably on noradrenergic neurotransmission. Although intriguing, this hypothesis still warrants further investigation and should not discourage physicians or patients from using SSRIs to manage MDD during the postmenopausal years. In a recent study investigating the use of the SNRI duloxetine in the treatment of depression in postmenopausal women, remission rates of 78.6% were obtained after 8 weeks of treatment.[44] Duloxetine also showed a positive effect in the amelioration of menopause-related symptoms.

Botanical agents have been investigated as nonhormonal alternatives for the treatment of menopause-associated symptoms, with limited evidence that these agents may in fact reduce the frequency and severity of vasomotor symptoms. Two small RCTs suggested that black cohosh (*Actaea racemosa*) is more effective than placebo in the treatment of mild to moderate vasomotor symptoms.[52,53] In a recent meta-analysis of 43 RCTs, soy isoflavone extracts showed a small positive effect over placebo after 12 weeks of treatment.[54] Newton and colleagues[55] tested the efficacy of 3 herbal regimens, hormone therapy, and placebo for the relief of vasomotor symptoms in a 1-year randomized double-blind trial (N = 353). Treatment groups included black cohosh alone (160 mg/d), multibotanical preparation including black cohosh (200 mg) and 9 other ingredients, multibotanical plus dietary soy counseling, conjugated equine estrogen, 0.625 mg (with or without medroxyprogesterone acetate), and placebo. At 12 months, symptom intensity was significantly worse with the use of multibotanical plus soy intervention than with placebo. Moreover, the difference in vasomotor symptoms between placebo and any of the herbal treatments at any time point in the study was minimal at less than 1 symptom per day. The only intervention that appeared to be efficacious compared with placebo was estrogen therapy.

To date, no studies have investigated the efficacy of botanical agents in the treatment of peri- and postmenopausal women with a major depressive episode. Nonetheless, 1 RCT that investigated 301 women with climacteric complaints showed a 41.8% improvement in Hamilton Depression Rating Scale (HAM-D) 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*).[56] 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) with climacteric symptoms, in which participants showed significant improvement of psychological and somatic symptoms.[57]

The available evidence indicates that transdermal estrogen, SSRIs, and SNRIs are effective in the treatment of depression during the menopausal transition; antidepressants, however, 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- and postmenopausal women are lacking. Women with a lifetime history of depression who are unable or unwilling to use hormone therapies may benefit from the mild effects of nonhormonal, nonpharmacological strategies for menopause-related symptoms. The presence of vasomotor symptoms and other menopause-related complaints seems to be associated with a higher risk for new onset or reemergence of depression during the menopausal transition.[27,30]

MANAGING ANXIETY DURING MIDLIFE

To date, no studies have systematically investigated the effects of hormonal therapies for the treatment of anxiety in perimenopausal or postmenopausal women. Some studies have assessed the effect of hormone therapies on symptoms of anxiety through secondary outcome measures. In a study of 70 women with climacteric symptoms, those who opted to receive HRT (N = 35) reported lower anxiety, sleep and somatic complaints compared with women who chose not to receive HRT (N = 35).[58] Three RCTs that assessed the secondary effects of HRT on anxiety symptoms in peri- and postmenopausal women reported little or no effects.[59–61] A large trial that randomized 419 postmenopausal women to 4 different HRT regimens found only modest effects of hormone treatments on anxiety scores after a long (up to 9 years) follow-up period.[62] However, these negative findings may be explained in part by a floor effect, because most study participants revealed relatively low anxiety scores at study entry.

Two studies investigated the effects of tibolone, a selective estrogen receptor modulator (SERM), on symptoms of anxiety and depression. One study compared 19 postmenopausal women using tibolone for 6 months with 25 women on no medication and found that tibolone had a positive effect in decreasing anxiety scores.[63] However, Hamilton Anxiety Rating Scale (HAM-A) scores decreased from 7.8 $\pm$ 7.7 at baseline to 5.5 $\pm$ 4.3 at 6 months, which may not have been clinically significant. In an RCT of 75 women who underwent surgical menopause for benign conditions, participants were randomized to receive tibolone, transdermal estradiol, or placebo and followed for 6 months. Improvement in anxiety and depression scores was observed with both active treatments compared with placebo; no differences between tibolone and transdermal estradiol were documented.[64] The relatively low baseline anxiety scores (HAM-A scores approximately 9–10) limit the generalization of these results. Studies including women with well-defined reproductive staging and high anxiety scores at study entry are necessary to better investigate the potential benefits of hormone therapies for the treatment of anxiety in midlife women.

Scarce data are available on the effects of antidepressants for the management of anxiety disorders in peri- and postmenopausal women; most data are derived from studies of healthy or depressed subpopulations. Nonetheless, existing evidence suggests that antidepressants may have a positive effect in alleviating anxiety symptoms among midlife postmenopausal women. Two open trials observed a modest anxiolytic effect with trazodone and paroxetine for the management of menopausal symptoms in otherwise healthy peri- and postmenopausal women.[65,66] Three open trials evaluated the effects of citalopram, venlafaxine, and duloxetine in peri- and postmenopausal women with major depression and reported reduction in anxiety scores as secondary outcome measures.[44,45,67] In all these studies, beneficial effects on depressive and anxiety scores were observed after 8 weeks of therapy. These antidepressants also had a positive effect in alleviating menopause-related symptoms, such as hot flashes and night sweats. Consistently, a study of perimenopausal women with depression reported a significant improvement in depression, anxiety, and menopause scores after 3 months of treatment with fluvoxamine (N = 53) or paroxetine (N = 52).[68] Although results with antidepressants are encouraging, future studies examining the efficacy of antidepressants in women with primary anxiety disorders in the context of menopause transition are warranted.

Several studies have investigated the use of botanical agents in the management of anxiety symptoms in peri- and postmenopausal women. In 1 RCT, 149 individuals (67% women) with a primary diagnosis of somatoform disorder were allocated to St. John's

wort or placebo and the HAM-A total score was used as the primary outcome measure.[69] A significant decrease in total HAM-A scores was observed after 42 days of treatment with St. John's wort. Two small RCTs evaluated the effects of kava extract on anxiety symptoms in peri-[70] and postmenopausal women[71]; the efficacy of kava extract plus calcium supplementation in reducing anxiety symptoms was superior than calcium supplementation only (control group).[70] The combination of kava extract + hormone therapy was more efficacious than hormone alone to alleviate anxiety symptoms in 40 postmenopausal women and this effect was maintained after 6 months of treatment.[71] Although preliminary, these findings suggest that kava extract may be a useful option in the management of anxiety during menopausal transition and the postmenopausal years. However, clinicians should be aware of the potential hepatotoxicity of kava extract as well as its various drug-drug interactions.[72] A small open trial tested the efficacy of Korean red ginseng on anxiety scores in 12 postmenopausal women with menopausal symptoms and found a small effect of this compound for the reduction of anxiety symptoms after 1 month of treatment.[73] Negative effects of *Ginko biloba* and *Panax ginseng* (Gincosan) on anxiety, mood, and menopausal symptoms were reported in an RCT involving 70 postmenopausal women.[74] More recently, 64 peri- and postmenopausal women were randomly allocated to either black cohosh or transdermal estradiol, and both treatments were equally effective in decreasing anxiety, depressive, and vasomotor symptoms.[75] Negative effects of isoflavones and valerian extract were reported by 2 RCTs.[76,77] In summary, studies investigating the effects of botanical agents in the management of anxiety in peri- and postmenopausal women are limited, given that anxiety scores were part of secondary outcome measures in most studies. Therefore, RCTs assessing peri- and postmenopausal women with well-defined anxiety disorders as primary diagnosis are necessary.

SUMMARY

Increasing evidence supports the notion that the menopausal transition may constitute a window of vulnerability for the development of mood and anxiety disorders; little is known, however, about the underlying mechanisms that contribute to the occurrence of this phenomenon. Moreover, 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 putative effect of menopause (natural or surgical) on psychological well-being, particularly among those who are unable or unwilling to use hormone therapies. More research on nonhormonal options (ie, SERMs, herbal supplements, and psychotropic agents) should be strongly encouraged to expand the portfolio of treatment strategies available for this population.

TREATMENT RECOMMENDATIONS

It is crucial that physicians and health professionals incorporate questions regarding reproductive status and past reproductive-related psychiatric events into their medical and psychiatric history. Antidepressants remain the treatment of choice for the management of most depressive and anxiety disorders during the perimenopausal and postmenopausal years. Nonetheless, the use of hormonal strategies, particularly estrogen-based therapies, has shown to not only improve depressive symptoms but also to promote alleviation of menopause-related complaints (eg, vasomotor symptoms, sexual dysfunction, sleep disruption) and better overall functioning and quality of life. Thus, the use of menopause-related hormone therapies,

either as an augmenting strategy or as a monotherapy (the latter for those who failed to have a considerable response/tolerability with conventional treatments), should be carefully considered.

Women are at a higher risk than men for developing depression and anxiety and such increased risk might be particularly associated with reproductive cycle events. Evidence suggests that the menopause transition constitutes a window of vulnerability for some women for new-onset and/or recurrent depression. Existing data supporting such risk and the putative underlying mechanisms contributing to this window of vulnerability are examined in this article. Moreover, hormonal and nonhormonal treatment strategies are critically reviewed, although more tailored treatment options for this population are still needed.

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