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Review

Depression and the menopause: why antidepressants are not enough?

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Abstract

Background. Gender differences, related to varying sexual hormone levels and hormone secretion patterns across the lifespan, contribute to women's vulnerability to mood disorders and major depression. Women are more prone than men to depression, from puberty onwards, with a specific exposure across the menopausal transition. However, controversy still exists in considering fluctuation/loss of estrogen as a specific aetiologic factor contributing to depression in perimenopause and beyond.

Aims. To briefly review the interaction between changes in menopausal hormone levels, mood disorders, associated neuropsychological co-morbidities and ageing, and to evaluate the currently available therapeutic options for perimenopausal mood disorders: (a) treatment of light to moderate mood disorders with hormonal therapy (HT); (b) treatment of major depression with antidepressants; (c) the synergistic effect between HT and antidepressants in treating menopausal depression.

Results. Depression across the menopause has a multifactorial aetiology. Predictive factors include: previous depressive episodes such as premenstrual syndrome and/or postpartum depression; co-morbidity with major menopausal symptoms, especially hot flashes, nocturnal sweating, insomnia; menopause not treated with HT; major existential stress; elevated body mass index; low socioeconomic level and ethnicity. Postmenopausal depression is more severe, has a more insidious course, is more resistant to conventional antidepressants in comparison with premenopausal women and has better outcomes when antidepressants are combined with HT.

Conclusion. The current evidence contributes to a re-reading of the relationship between menopause and depression. The combination of the antidepressant with HT seems to offer the best therapeutic potential in terms of efficacy, rapidity of improvement and consistency of remission in the follow-up.

Keywords: Mood disorders, depression, menopause, menopausal symptoms, hormonal therapy, antidepressants

Introduction

Mood disorders encompass a spectrum of symptoms varying from mild mood changes to severe, major depression. Although the most serious of depressive illnesses in the elderly is major depressive disorder (MDD), perimenopausal women's quality of life can be significantly impacted by dysphoric disorder, subthreshold depression (minor depression) or a depressive disorder due to a general medical condition, all of which have been shown to be more prevalent than major depression in the community dwelling population of older adults.

Menopausal women are also more likely to develop grief reaction and frequently deal with issues of bereavement.[1] Women are indeed more vulnerable to mood disorders in the years after puberty. Gender differences, related to varying sexual hormone levels and secretion patterns across the lifespan, contribute to women's vulnerability to mood disorders and major depression.[2–4] The menopausal transition is considered a specific 'window of vulnerability' to mood disorders. However, controversy still exists in considering the fluctuation/loss of estrogen as a specific aetiologic factor contributing to depression in perimenopause and beyond.[5–28]

The aims of this concise study are: (1) to briefly review the interaction between: (a) sexual hormones and neuronal functioning and (b) changes in menopausal hormone levels, mood disorders, associated neuropsychological co-morbidities and aging; (2) to summarize the characteristics of the menopausal depression and (3) to evaluate the currently available therapeutic options of perimenopausal mood disorders focusing only on their pharmacological treatment: (a) treatment of light to

moderate mood disorders with hormonal therapy (HT); (b) treatment of depression with antidepressants; (c) the synergic effect between HT and antidepressants in treating menopausal major depression, (d) role of antidepressant in treating menopausal symptoms, an opportunity relevant to the clinical practice, when HT is not feasible (e.g. breast cancer patients) or not desired.

Sexual hormones and neuronal functioning

Estrogens and neuroplasticity
Accumulated evidence indicates that ovarian hormones regulate a wide variety of non-reproductive functions in the central nervous system, by interacting with several molecular and cellular processes.[29]

Estrogens exert many roles on the brain, by modulating homeostasis, synaptic plasticity and neuronal protection.[30] Estrogens exert their effects via a slower genomic mechanism of action involving binding of estrogen to nuclear estrogen receptors and subsequent regulation of transcription, and via a more rapid non-genomic membrane pathway through calcium, ion channel and kinase signalling.[31] Estrogens demonstrated to possess a strong neurotrophic effect: they optimize the neuronal membranes' reparation, increase the dendritic sprouting and the synthesis, release and action of neurotransmitters.[32] Evidence indicates as well a specific anti-inflammatory action on the brain.[33,34]

Androgens and neuroplasticity
Androgens have a strong trophic effect on female brain, both directly and through the conversion to estrogens through the aromatases[35]

Progestins and neuroplasticity
Many studies demonstrate the synergic effect between estrogens and progestins on neuroplasticity,[36,37] especially in reparative functions.[32] Some *in vitro* studies confirm this effect.[38]

Changes in menopausal hormone levels, mood disorders and associated co-morbidities

Chronic estrogen deficiency has a negative effect on the brain major systems: the neurovegetative,[6,7] the emotional/affective,[6–8] the cognitive and motor.[9–12] The symptoms that women complain of across the menopause and beyond show a different onset and time pattern, according to the type of neuronal damage the estrogen loss causes over time:

- Early neurovegetative symptoms such as hot flushes, insomnia, night tachycardia are consequent to the rapid disregulation of the hypothalamic set-points secondary to the impact of estrogenic fluctuations on neuronal functioning in the short term;
- Early affective symptoms, such as depression and anxiety, are due to the impact on the limbic system of both the estrogenic fluctuations, leading to a reduction of key neurotransmitters such as serotonin, dopamine and endorphins,[4,5] as well as environmental factors, across the menopause;
- Late cognitive and motor symptoms express the long-term effect the estrogen losses, and other biological damaging factors, have on neuronal survival.[5] Indeed, these symptoms appear when the majority of cholinergic and dopaminergic neurones, respectively, have been destroyed.

Estrogen fluctuations and loss are the common denominator of a complex and persistent functional and structural brain damage across and after the menopause. This is the pathophysiologic aetiology of different and severe co-morbidities: severe hot flushes, sleep alterations and depression,[6,7] Parkinson's and Alzheimer's diseases,[8–10] which well express the general brain vulnerability to the estrogen deficiency in the short- and long-term. Depression is indeed a predictive factor for other neurodegenerative pathologies such as Alzheimer and Parkinson's diseases, which are associated with cerebral aging, specific damaging factors and estrogenic deficiency. Moreover, two recent studies demonstrated that iatrogenic premature menopause significantly, without estrogen replacement, increases the risk of Alzheimer[11] and Parkinsonism, with a borderline significance for Parkinson's disease.[12] Women who underwent either unilateral or bilateral oophorectomy before the onset of menopause have an increased risk of cognitive impairment or dementia. The risk is increased with younger age at oophorectomy.

Characteristics of menopausal depression

Mood disorders in middle-aged women are a significant cause of morbidity and disability.[13,14] Menopausal depression has atypical manifestations, such as a more insidious onset and course, and a multifactorial aetiology that can make it difficult to recognize and treat it with an aetiologically focused approach.[15,16] Moreover, menopausal symptoms may exacerbate depressive symptoms and *vice versa*.[17]

The causal correlation between depressive symptoms and menopause is still a matter of debate. A major controversy is to establish whether the depression is caused by psychological/environmental factors related to the life-cycle-related events and ageing of the woman or whether the hormonal changes can have a specific influence on this condition.

Many studies of the 1990s deny this correlation.[18–21] Others demonstrate that depressive symptoms decrease with the increase of woman's age,[6] suggesting that age can have a protective effect after the menopause. This perspective is currently considered obsolete, particularly when co-morbidity between depression and neurodegenerative diseases is considered.[22–25] More recent studies highlight an increased incidence of depression in women during the menopausal transition.[22,12] Moreover, women who enter the menopausal transition early are at higher risk of developing depression.[24]

Recent studies demonstrate a relation between the perimenopausal reduction of sexual hormones and an increased vulnerability to mood disorders even in women

who never experienced it before.[25] This discrepancy is more likely due to the differences in the research methodology that is currently more rigorous with the use of validated instruments. Current evidence supports a specific role of the estrogen deficiency in contributing to major depression.

These studies demonstrate that menopause may be considered as a time frame of vulnerability during which women are at higher risk to develop depression, as in other periods of women's life cycle, such as the premenstrual days and immediate postpartum.[2]

Independent predictors for menopausal depression are: episodes of depression in fertile age; premenstrual syndrome; postpartum depression; co-morbidity with main menopausal symptoms like hot flashes and insomnia; elevated body mass index (BMI); poor social status; and ethnicity.[15]

Moreover, women who undergo bilateral oophorectomy without receiving replacement estrogens are more likely to suffer from major depression.[26,27]

The Structured Clinical Interview for DSM-IV Axis I Disorders (SCID) was used to assess diagnoses of lifetime, annual and current major depression in a community-based sample of premenopausal or early perimenopausal African-American and white women.[28] Over seven years of follow-up, 42 (15.8%) women met criteria for a diagnosis of major depression.

Risk factors were:

- Frequent vasomotor symptoms (VMS; hot flashes and/or night sweats) (hazardous ratio [HR] 2.14, $P = 0.03$) were a significant predictor of major depression in univariate analyses;
- Lifetime history of an anxiety disorder (HR 2.20, $P = 0.02$);
- Role limitations due to physical health (HR 1.88, $P = 0.07$) at baseline;
- A very stressful life event (HR 2.25, $P = 0.04$) prior to depression onset predicted a first episode of major depression;
- Use of psychoactive substances;
- Elevated BMI;
- Poor social status.

In a multifactorial reading of the aetiology of perimenopausal depression, estrogen' fluctuation and loss may act as a *predisposing factor*, when they increase limbic vulnerability to environmental stressors; as a *precipitating factor*, when they trigger the expression of a genetic vulnerability to major depression; as a *maintenance factor*, when lack of appropriate HT worsens neuronal vulnerability to both genetic and environmental factors.

Hormonal treatment of menopausal mood disorders

Based on current knowledge, estrogen treatment for affective disorders may be efficacious in two situations: (i) to stabilize and restore disrupted homeostasis – as occurs in premenstrual, postpartum or perimenopausal conditions[2]; and (ii) to act as a psychomodulator during periods of decreased estrogen levels and increased vulnerability to dysphoric mood, as occurs in postmenopausal women. There is growing evidence suggesting that estrogen may be efficacious as a sole antidepressant for depressed perimenopausal women.[39,40] HT alone seems to be effective in mild to moderate depression, while antidepressant drugs are needed in major depression. Women willing to use hormone replacement therapy (HRT) during the menopause may receive higher benefits in mood.

Estrogen treatment, even in non-depressed individuals, enhances platelet 3H-imipramine binding and improves Beck Depression Inventory (BDI), a test that detects mild to severe depressive symptoms.[41] Psychological functioning improves in asymptomatic peri- and postmenopausal women undergoing estrogen therapy (ET).[42] Short-term continuous HRT regimens improve mood scores.[43] Onalan *et al.* evaluated the long-term effects of the combined HRT on depressive symptoms in postmenopausal women. In this prospective-randomized, placebo-controlled, double-blind study, 286 women in menopause were divided into four groups according to therapeutic regimens they received; (1) conjugated equine estrogen (CEE) of 0.625 mg plus medroxyprogesterone acetate (MPA) of 2.5 mg ($n = 79$), (2) CEE (0.625 mg) plus MPA of 5 mg ($n = 77$), (3) tibolone of 2.5 mg (a selective tissue estrogenic activity regulator) ($n = 76$) and (4) calcium (Ca) of 1000 mg ($n = 54$). BDI was assessed before and after 12 months of treatment with oral continuous HRT and Ca supplementation. BDI scores decreased significantly in all HRT groups after 12 months of treatment, compared with Ca group ($P < 0.05$). Continuous combined hormone replacement regimens, CEE + MPA and tibolone have superior long-term effects on mood scores in the menopause and should be considered during the decision process for use of HRT due to menopausal symptoms.[44]

Antidepressants in the treatment of postmenopausal depression

Specifically, postmenopausal depression is more severe, has a more insidious course, is more resistant to conventional antidepressants in comparison with the premenopausal women and has better outcomes when antidepressants are combined with HT.[45]

It has been suggested that a chronic hypoestrogenic state may reduce the response to antidepressant drugs. Thirty-nine female patients ($n = 17$ in premenopause; $n = 22$ in postmenopause) with MDD based on DSM-IV criteria, who were not on HRT, participated in the study in order to prospectively evaluate the effect of menopausal status and its hormonal correlates on the effectiveness of antidepressant treatment for six weeks. After controlling for age, age at onset, baseline symptom severity, antidepressant dosage and hormonal levels of follicle-stimulating hormone (FSH), luteinizing hormone (LH) and estradiol (E2), postmenopausal women showed a poor response to antidepressants over six weeks of treatment, compared with the response of premenopausal women. Old age and high levels of FSH were also associated with the efficacy of antidepressants in postmenopausal women. Menopausal status and old age are

predictors of a poor response to antidepressant treatment. Furthermore, the FSH may interfere with the mechanism of action of the antidepressant agents.[45]

Another study investigated the role of menopausal status including the level of sex hormones on cognitive function during antidepressant treatment. Thirty-nine female patients ($n = 17$ in premenopause; $n = 22$ in postmenopause) with MDD based on DSM-IV criteria and who were not on hormonal replacement therapies participated in a prospective, six-week, open-label naturalistic study. The Hamilton rating scale for Depression (HAMD), Montgomery–Asberg Depression Rating Scale and the Cognitive Failure Questionnaire (CFQ) were administered at baseline, week 1, week 3 and week 6. Levels of FSH, LH and E2 were collected at baseline visit. Cognitive functioning improved during antidepressant treatment in the overall sample ($P = 0.00001$). In postmenopausal women, E2 levels were strongly correlated with CFQ scores at each measurement. After controlling for depression severity, E2 levels maintained a significant association with the baseline CFQ scores (regression analysis: beta $= -0.55$ $P = 0.010$; correlation: $R = -0.54$). In addition, the reduction of CFQ scores during antidepressant treatment was significantly associated with E2 levels ($P = 0.021$), independently of the improvement of depressive symptoms, which, however, had a strong effect ($P = 0.0003$). Nevertheless, there was no association of CFQ score with sex hormones in premenopausal women. In postmenopausal women, the CFQ scores were correlated with E2 levels and the reduction of CFQ score during antidepressant treatment was also dependent on E2 levels, even controlling for depressive symptoms severity. The present study further supports a crucial role of E2 on the affective and cognitive function in postmenopause women. Moreover, these results suggest that E2 may influence the improvement of cognitive function in postmenopausal women with MDD, during treatment with antidepressants.[46]

Synergy between antidepressants and HRT

An increasing body of evidence suggests that a hypoestrogenic postmenopausal status increases the vulnerability to depression and decreases the effect of antidepressant drugs.[45,47,48] Animal studies support the synergistic role of estrogen and selective serotonin reuptake inhibitor (SSRI) in optimizing the antidepressant response, evaluated through specific behavioural tests.[49]

In line with this pathophysiologic reading, Thase *et al.* investigated whether differences in antidepressant efficacy are moderated by an interaction of age and gender. A pooled dataset from eight randomized, controlled trials of patients with MDD was re-analysed to compare remission rates following therapy with venlafaxine ($n = 851$), one of the several SSRIs ($n = 748$) or placebo ($n = 446$). Remission was defined as a final HAMD score = 7. Pairwise comparisons were conducted using stepwise multiple logistic regression models with main effect and interaction terms for treatment, sex and age (younger: <50; older: >50). Among older women, the impact of HRT on remission rates was also examined. Remission rates on venlafaxine therapy were not affected by age, sex or HRT use. Among women there was a significant interaction reflecting poorer SSRI response in the older age group (Wald chi-square = 4.21, df = 1, $P = 0.04$); HRT appeared to eliminate this difference. Although the advantage in remission rates favouring venlafaxine was modest for younger women (6–9%), the difference among older women not taking HRT was 23%. These findings provide further evidence that age, gender and HRT moderate response to antidepressant medications.[50]

ET may also play a role on antidepressant response in postmenopausal women with MDD by:

- *Accelerating the antidepressant response*: Rasgon *et al.* conducted a study in which 22 subjects received sertraline at 50 mg/day for one week, with an increase to 100 mg/day at week 2 for a 10-week trial. Transdermal estrogen or placebo patches 0.1 mg were randomly administered concurrent with the initiation of sertraline treatment. The 21-item Hamilton Depression Rating Scale (HDRS-21) was administered to all patients at baseline and weekly thereafter. Both groups showed a similar significant reduction in HDRS-21 scores by the end of the study. There was no significant difference between the two treatment groups at the end of the 10-week trial, but the women receiving sertraline with ET showed significantly greater early improvement (weeks 2–4) compared with the women receiving sertraline with placebo.[51]
- *Potentiating antidepressant medication effect improving mood*: Morgan *et al.* investigated the effects of estrogen augmentation on mood and memory in women with perimenopausal depression who had experienced a partial response to antidepressant medications. Women receiving estrogen had a significantly larger decrease in HAM-D scores than women receiving placebo ($t = 2.86$, df = 15, $P = 0.012$). Group differences in tests of verbal memory were not significant, although improved scores in verbal memory were significantly correlated with a decrease in FSH ($P = 0.021$). Short-term, low-dose estrogen augmentation of antidepressant medication was significantly associated with the improved mood, but not memory, in perimenopausal women with MDD in partial remission.[52] Westlund Tam *et al.* presented a study in which five perimenopausal women diagnosed with major depression were randomly assigned to one of three treatment conditions: (1) fluoxetine 10–20 mg alone, (2) estradiol patch 0.1–0.2 mg alone or (3) the combination of fluoxetine 10–20 mg and estradiol patch 0.1–0.2 mg. The combination of fluoxetine and estradiol was most effective, followed by fluoxetine alone and then estradiol alone.[53]
- *Demonstrating a specific efficacy:* In those depressive disorders with iatrogenic menopause consequent to chemotherapy.[54]

Improvement of menopausal symptoms with antidepressant drugs

Antidepressants can reduce some menopausal symptoms when they act on common neuro-biological common

denominators. Soares *et al.*[55] found a similar efficacy between HT and escitalopram in curing depressive symptoms and menopausal symptoms such as vasomotor symptoms and insomnia.

After HT discontinuation, paroxetine offers better control of menopausal hot flushes than placebo,[56,57] and may be useful for those women who have a contraindication to HRT,[58–62] such as breast cancer patients, or those who prefer to stop HT and address their neurovegetative and affective symptoms in a non-hormonal way. However, it should be remembered that SSRI address only a few neurovegetative symptoms, besides depression, but cannot modulate the many others symptoms caused by the estrogen loss (such as joint pain, vaginal dryness, worsened urge incontinence, etc.).

Conclusion

The current evidence contributes to a re-reading of the relationship between menopause and mood disorders. Estrogen fluctuations and loss contribute to mild–moderate depression. Estrogen loss modulates some specific characteristics of postmenopausal major depression, such as the insidious onset, the severity of course, the reduced response to conventional antidepressants in comparison to the premenopausal year. While HT alone can improve mild to moderate mood disorders, the combination of antidepressant with HT seems to offer the best therapeutic potential for major postmenopausal depression in terms of efficacy, rapidity of improvement and consistency of remission in the follow up. Further controlled studies are needed to confirm this role of loss of sexual hormones in the modulation of severity of postmenopausal depression and the potential synergic role of HT with antidepressant to obtain a more satisfactory and persistent therapeutic result.

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