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Depression and the menopause: why antidepressants are not enough?

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Abstract

Background
Gender differences, related to a different sexual hormones levels and hormone secretion patterns across the lifespan, contribute to the specific 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 the fluctuation/loss of estrogen as a specific etiologic factor contributing to depression in perimenopause and beyond.

Aims of the study
1) To briefly review the interaction between changes in menopausal hormone levels, mood disorders, associated neuropsychological comorbidities, and aging;
2) 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 antidepressant; c) the synergistic effect between HT and antidepressants in treating menopausal depression.

Results
Depression across the menopause has a multifactorial etiology. Predictive factors include: previous depressive episodes such as premenstrual syndrome and/or post-partum depression; comorbidity 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 antidepressant are combined with HT.

Conclusion
The current evidence contributes to a re-reading of the relationship between menopause and depression. The combination of 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.

Introduction

Mood disorders encompass a spectrum of symptoms varying from mild mood changes to severe, major depression. While the most serious of depressive illnesses in the elderly is major depressive disorder, perimenopausal women's quality of life can be significantly impacted by dysphoric disorder, sub-threshold 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 a different sexual hormone levels and secretion patterns across the lifespan, contribute to the specific 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 etiologic factor contributing to depression in perimenopause and beyond. [5-28]

The aim of this concise study is:

1) to briefly review the interaction between: a) sexual hormones and neuronal functioning; b) changes in menopausal hormone levels, mood disorders, associated neuropsychological co-morbidities, and aging;
2) to summarize the characteristics of the menopausal depression;
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; b) treatment of depression with antidepressant; c) the synergic effect between hormonal therapy 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 (eg 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 CNS, 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 signaling. [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 neuro-transmitters. [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 comorbidities

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 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 symptom, 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 estrogens loss, and other biological damaging factors, have on neuronal survival [5]. Indeed these symptoms appear when the majority of cholinergic and dopaminergic neurons, 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 etiology of different and severe comorbidities:

- severe hot flushes, sleep alterations and depression [6, 7]
- depression, Parkinson's and Alzheimer's disease [8-10] , that well express the general brain vulnerability to the estrogen deficiency in the short and long term. Depression is indeed a predictive factor for other neuro-degenerative pathologies as Alzheimer and Parkinson's diseases, which are associated with cerebral aging, specific damaging factors and to 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-age 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 etiology which can make it difficult to recognize and treat it with an etiologically 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 whereas the depression is caused by psychological/environmental factors related to the life-cycle related events and aging of the woman or if the hormonal changes can have a specific influence on this condition.
Many studies of the nineties 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 comorbidity 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 pre-menstrual days and immediate post-partum. [2]

Independent predictors for menopausal depression are: episodes of depression in fertile age, premenstrual syndrome, post-partum depression; co-morbidity with main menopausal symptoms like hot flashes and insomnia; elevated 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 7 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) (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 etiology 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 hormonal therapy 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 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 which detects mild to severe depressive symptoms [41]. Psychological functioning improves in asymptomatic peri- and postmenopausal women undergoing estrogen therapy [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 1,000 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 to 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]

Antidepressant 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 antidepressant are combined with hormonal therapy [45]

It has been suggested that a chronic hypoestrogenic state may reduce the response to antidepressant drugs. Thirty-nine female patients (n17 in pre-menopause; n22 in post-menopause) with major depressive disorder 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 6 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), post-menopausal women showed a poor response to antidepressants over 6 weeks of treatment, compared to the response of pre-menopausal women. Old age and high levels of FSH were also associated with the efficacy of antidepressants in post-menopausal 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 pre-menopause; n=22 in post-menopause) with MDD based on DSM-IV criteria and who were not on hormonal replacement therapies participated in a prospective, 6-week, open-label naturalistic study. The Hamilton rating scale for Depression (HAMD), Montgomery-Asberg Depression Rating Scale (MADRS) and the Cognitive Failure Questionnaire (CFQ) were administered at baseline, week 1, week 3, and week 6. Levels of follicle stimulating hormone (FSH), luteinizing hormone (LH) and estradiol (E2) were collected at baseline visit. Cognitive functioning improved during antidepressant treatment in the overall sample (P=0.00001). In post-menopausal 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 from 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 pre-menopausal women. In post-menopausal 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 post-menopause women. Moreover, these results suggest that E2 may influence the improvement of cognitive function in post-menopause 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 SSRI in optimizing the antidepressant response, evaluated through specific behavioral 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 major depressive disorder (MDD) was reanalyzed to compare remission rates following therapy with venlafaxine (*n* = 851), one of several selective serotonin reuptake inhibitors (SSRIs) (*n* = 748), or placebo (*n* = 446). Remission was defined as a final Hamilton Rating Scale for Depression (HAM-D) 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 also was 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. Whereas the advantage in remission rates favoring 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]

Estrogen therapy (ET) may also play a role on antidepressant response in postmenopausal women with major depressive disorder by:

1) Accelerating the antidepressant response: Rasgon et al conducted a study in which twenty-two 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 to the women receiving sertraline with placebo 51.
2) 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 Hamilton Rating Scale for Depression (HAM-D) scores than women receiving placebo (t = 2.86, df = 15, p = .012). Group differences in tests of verbal memory were not significant, although improved scores in verbal memory were significantly correlated with a decrease in follicle-stimulating hormone (p = .021). Short-term, low-dose estrogen augmentation of antidepressant medication was significantly associated with 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.
3) ET demonstrates a specific efficacy in those depressive disorders with iatrogenic menopause consequent to chemotherapy 54.

Improvement of menopausal symptoms with antidepressant drugs

Antidepressant can reduce some menopausal symptoms when they act on common neuro-biological common denominators. Soares and Coll found a similar efficacy between HT and escitalopram in curing depressive symptoms and menopausal symptoms such as vasomotor symptoms and insomnia [55].

After hormone therapy discontinuation, paroxetine offers a 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 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, beside depression, but cannot modulate the many others symptoms caused by the estrogen loss (such as joint pain, vaginal dryness, worsened urge incontinence, etc)

Conclusions

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. Estrogens loss modulate 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 hormone therapy 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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