Treatment of Mood Disorders in Midlife Women

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Objectives

- Understand Incidence of Mood Disorders in Midlife Women
- Discuss Pathophysiology of Mood Disorders in Midlife Women
- Identify Appropriate Treatment Options of Mood Disorders in Midlife Women

Today’s Focus: Midlife Women

- Midlife women=Menopausal transition (MT)=Perimenopause=Climacteric
- Includes time frame between full reproductive function and menopause
  (Del et al. Menopause and Mood, 2000)
  - Time frame typically 4-8 years in length
  - Typically occurs in 45-55 year old women
  - Average age 47 years old

**Epidemiology**

- Mood disorders are twice as common in women as in men
  - Prevalent at all ages
  - Peak in adolescence and equalizes after menopause
- 15-50% of women experience depressive symptoms during the menopausal transition (MT) (Gelfand et al., Menopause. 2015)
  - 15-30% meet criteria for depressive disorders
  - There is a 2x increased risk of a first episode of depression for women in MT
- SWAN study showed women 2-4x more likely to experience MDD if they were perimenopausal or early postmenopausal (Bromberger et al., Psych Med. 2011)
- Seattle midlife Women’s Health Study found a doubling of the rate of depressive symptoms in late MT (Wood et al., Menopause. 2008)

**Risk Factors for Mood Disorders in Midlife**

- Prior depressive episode *
  - Especially if related to pre-reproductive event (Soares, Menopause. 2014)
- Significant vasomotor symptoms
- Psychosocial stressors
  - Financial stress
  - Changes in work-life
  - Divorce, Children leaving for college, Caring for elderly parents
- Health related issues

**Pathophysiology of Mood Disorders in Midlife**

- Domino theory
  - Vasomotor symptoms trigger depressed mood due to disruption in sleep and functional impairment (Gordon et al., Curr Pain Head. 2014)
  - Hot flushes provoke sleep disturbance which affects mood
- Empty Nest Syndrome
  - Women become more aware of their loss of fertility and their maternal role
  - Changes in family dynamic, changes in work life, changes in financial security occur at the same time as MT and may cause depressive symptoms
**Pathophysiology of Mood Disorders in Midlife**

- Hormonal fluctuation
  - Evidence of worsening of mood disorders during times of hormonal fluctuation
  - Related to menstruation of women, premenstrual dysphoric disorder (PMDD)
  - Related to pregnancy or postpartum
  - Related to menopausal transition
  - History of PMDD and/or postpartum depression is a risk factor for depression during menopause (Overland et al., Menopause, 2009; Freeman, Arch Gen Psych, 2004)
  - Evidence that incidence of depression in postmenopausal-aged women is similar to that of men
    - Although estrogen levels are low, the levels of estrogen are stable and not fluctuating

- Abrupt changes in hormone levels may alter the equilibrium of neurotransmitters found in the brain thus increasing risk of mood disorders
  - ESTROGEN

**Role of Estrogen in Treatment of Mood Disorders in Midlife Women**

- Modulates serotonin and norepinephrine
- Increases GABA activity
- Decreases activity of MAO (involved in serotonin degradation)
- Increases tryptophan hydroxylase (involved in serotonin synthesis)
- Selectively increases serotonin receptor density in the brain
- Promotes NE availability
- Involved in increasing NE hydroxylation from dopamine
  (Suarez, Menopause, 2014)

**Diagnosis of Major Depressive Disorder**

**DSM V Diagnostic Criteria (5 symptoms for 2 week period)**

- Depressed mood or anhedonia *
  - Changes in sleep
  - Loss of interest/pleasure
  - Guilt/worthlessness
  - Fatigue/loss of energy
  - Decreased focus or concentration
  - Changes in appetite or weight
  - Changes in activity (psychomotor)
  - Thoughts of death/suicide
Treatment Options for Women in MT

- Psychotherapy
  - Cognitive-Behavioral Therapy
- Complementary medicine
  - Acupuncture
- Antidepressants
  - SNRI
  - SSRI
  - Estrogen
  - Oral
  - Transdermal

Therapy

- Cognitive-Behavioral Therapy (CBT)
  - CBT offers improvement in hot flushes and night sweats by changing the cognitive appraisal of symptoms (Blonk et al., Menopause. 2014)
  - Telephone guided self-help CBT improved symptoms of hot flushes and night sweats (Skerbeková et al., Maturitas. 2014)

Complementary Medicine

- Acupuncture
  - No clear evidence of improvement of vasomotor symptoms or mood in perimenopausal women (Cho et al., Menopause. 2009, Dodin et al., Cochrane Data Base Syst Rev. 2013)

Antidepressants

- Side Effects (15-20% of patients)
  - GI symptoms (nausea)
  - Sexual dysfunction (20%)
  - Headache
  - Sleep disturbance
  - Should see improvement in symptoms within 1 month

- Antidepressants
  - SNRI
    - Duloxetine (20-60 mg)
    - Venlafaxine (37.5-225 mg)
  - SSRI
    - Fluoxetine (10-40 mg)
    - Sertraline (50-150 mg)
    - Citalopram (20-40 mg)
    - Escitalopram (10-20 mg)
    - Paroxetine (20-50 mg)
Antidepressants: SNRI vs SSRI

- In a pooled analysis, SNRIs showed higher remission rates than SSRIs (Entsuah et al. J Clin Psychiatry 2001).
- Good evidence of improvement in symptoms with citalopram, escitalopram, paroxetine, venlafaxine as monotherapy.
- If a woman has had success in the past with a certain antidepressant should start with that antidepressant as 1st line regardless of class.
- If a woman is taking tamoxifen should use SNRI instead of SSRI due to concern about interference with metabolism of tamoxifen with SSRIs (Stubbs et al. J Clin Psychiatry. 2005). CYP2D6 inhibitors paxitine, fluoxetine.

Role of Estrogen in Treatment of Mood Disorders in Midlife Women

- Estrogen as treatment.
  - Postmenopausal women with MDD treated with estradiol monotherapy have improvement in mood similar to that with antidepressants.
  - Transdermal estradiol (50-100 microgram/day) resulted in 60-75% of subjects noting partial or total remission in depressive symptoms compared to 20-30% of subjects receiving placebo (Soares et al. Arch Gen Psychiatry. 2001, Schmidt et al. Am J Obstet Gynecol. 2000).
  - Postmenopausal women do not have the same improvement in depressive symptoms with estradiol monotherapy.
  - Data show estradiol may be used as augmentation for women with inadequate response to antidepressants alone.
  - Estrogen treatment should show improvement within the 1st month of use.

Role of Progestins in Treatment of Mood Disorders in Midlife Women

- Adding a progestin to estrogen therapy may attenuate the beneficial effects of estrogen on mood (Kious. Menopause. 2014).
- Increases concentration of MAO causing decrease in serotonin concentration (Santorelli et al. Affective Disorders, 2003).
- Opposite effect from estrogen.
- For women with intact uterus.
- Cyclic use of progestins may be less harmful to mood in women who respond well to estrogen (Cohen et al. Amer J Med 2005).
- Levonorgestrel IUD may be another option.

Treatment Strategies

- How to decide which treatment.
  - Mood symptoms and vasomotor symptoms frequently coincide.
  - Primary mood symptoms- SNRI, SSRI.
  - Primary vasomotor symptoms- estrogen.
  - Consider dual therapy with antidepressant and estrogen.
  - If patient responds to test estrogen protocol.
  - Both symptoms equally bothersome: consider dual therapy with antidepressant and estrogen.
Other Considerations

- Women in menopause transition may still ovulate
- Menopausal doses of estrogen and progestrone may not suppress ovulation
- Consider levonorgestrel IUD plus estrogen
- Consider estrogen-progestin formulations with sufficient dose of progestin to suppress ovulation
  - EE 5 mcg/NETA 1mg
  - E2 1 mg/NETA 0.5mg

Conclusions

- Mood disorders in midlife women can be debilitating
- There are many options for treatment
  - Hormonal
  - Psychotropic
  - Therapeutic
  - Combination of above