Menopausal Depression and PMDD

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Lecture Content

- PMDD and Related Conditions
- Treatments for PMDD/PMS
- Lifestyle/“Natural” Treatments
- Depression during the Menopausal Transition and Associated Symptoms

Definitions

- **PMS**
  - Premenstrual emotional, behavioral, and physical symptoms; remit after menses; mood changes generally minor
  - Majority of women; do not usually need medical or psychiatric intervention
- **PMDD**
  - DSM-5 diagnosis, signifies significant psychiatry morbidity; interference with function
- **Other psychiatric disorders**
  - May have cyclic exacerbations of other DSM disorders (PME)

PMDD

- ≥5 during most menstrual cycles during last week of luteal phase (remit within days of onset of menses)
  - Depressed mood
  - Anxiety
  - Lability
  - Irritability
  - Decreased interest
  - Poor concentration
  - Decreased energy
  - Change in appetite
  - Change in sleep
  - Feeling overwhelmed
  - Other physical symptoms (bloating, breast pain, headaches)
- Interferes with function, activities, relationships
- Not merely an exacerbation of another disorder
- 3% to 5% of women

Prenumstrual Mood Problems: Risk Factors

- Age: onset typical in late 20s to mid-30s
- History of psychiatric disorder(s)
  - Increased risk in individuals with history of major depression, postpartum mood episodes, bipolar disorder
- Family history
- Psychosocial stressors

Core Premenstrual Symptoms

- Most consistent symptoms across cycles
  - Anxiety
  - Irritability
  - Mood lability

PMDD and Neurobiology

- Higher allopregnanolone levels (neuroactive progesterone metabolite) in women with PMDD, lower cortisol levels
- Normal ovarian function appears to trigger symptoms in some vulnerable individuals

Screening and Diagnosis

- History
- Prospective documentation—prospective daily mood ratings (at least 2 months)

Treatments for PMDD/PMS

SSRIs for PMDD

- Cochrane Database Systematic Reviews (2009 and 2013): Reviews of efficacy of SSRIs in severe PMS/PMDD
- Selection criteria:
  - Trials with prospective diagnosis of PMS, PMDD, or LPDD; randomized to SSRI or placebo
- Results:
  - SSRIs highly efficacious compared to placebo ($P < .00001$)
  - Secondary analysis: efficacious on symptom subsets: physical, functional, behavioral ($P < .00001$ each)
  - Luteal phase only and continuous administration both effective
  - All SSRIs efficacious: fluoxetine, paroxetine, sertraline, fluvoxamine, citalopram, and clomipramine
  - Withdrawals due to side effects were twice as likely with SSRI compared to placebo ($P < .00001$)
  - Small to moderate effect sizes: $-0.36$ with change score, $-0.65$ with end scores

Antidepressant Dosing Strategies

- Relatively lower doses may be enough
- Dosing options:
  - Daily
  - Daily with higher dosing premenstrually
  - Intermittent, scheduled
  - Intermittent PRN
Reproductive Hormones

- Estrogen appears beneficial
- In general, progesterone ineffective in some controlled studies (despite anecdotal reports), may even worsen symptoms
- Mixed results with oral contraceptives
  - For women on oral contraceptives, type of progesterone may affect PMS

Oral Contraceptives for PMDD

- COCs have both progestin and estrogen; recent studies in COCs containing drospirenone and low estrogen (approval for treating PMDD)
- Cochrane Review (2012)
  - 5 trials, N = 1920. 2 placebo-controlled trials of women with PMDD showed less severe premenstrual symptoms after 3 months with drospirenone (plus EE 20 g) than with placebo
  - The drospirenone group had greater decreases in impairment of productivity, social activities, and relationships
  - Side effects: nausea, intermenstrual bleeding, breast pain
  - Conclusions: Drospirenone 3 mg (plus EE 20 g) may help treat premenstrual symptoms in women with severe symptoms (ie, PMDD). The placebo also had a large effect. Not known whether the COC works after 3 cycles, helps women with less severe symptoms, or is better than other oral contraceptives

Oral Contraceptives for PMDD

- Best studied in
  - Short trials (3 cycles)
  - Severe premenstrual dysphoria/PMDD
- Limitations
  - Placebo responses, need more long-term studies, unclear regarding add-on benefits to antidepressants
  - Safety: not considered safe in women > 35 who smoke
- Response rate may be modest compared with placebo
  - COC responders: 48%
  - Placebo responders: 36%
  - Number needed to treat: 8

Lifestyle/“Natural” Treatments

Question: Which of the following integrative/lifestyle treatments has the best evidence for use as an adjunct in women with premenstrual symptoms/PMDD?

A. Exercise
B. Omega-3 fatty acids
C. Calcium
D. Bright light therapy
E. Dark chocolate

Light Therapy

- Reduction of depressive symptoms in PMDD reported, small amount of data
- May decrease carbohydrate cravings along with improved mood
- Evidence limited to date, may have small effect size
- Small number of trials, small number of participants, unclear efficacy

Reference:


Exercise

- Observational studies suggest women who exercise experience less emotional distress premenstrually
- Intervention studies (reviewed by Daley, 2009)
  - 4 intervention studies, small number of participants; promising preliminary data
  - Adequately powered, controlled studies needed
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Calcium

- Calcium: impact on premenstrual symptoms
  - Including mood symptoms
  - Approximately 500 to 1500 mg/day
  - Large study N = 497
  - Calcium carbonate 1200 mg/day or placebo
  - 48% reduction in calcium group, 30% in the placebo group (included affective symptoms)
  - Calcium regulation may be altered in women with PMDD across cycle

Omega-3 Fatty Acids and Premenstrual Symptoms

- Omega-3 fatty acids: treatment with fish oil (1.8 g/day EPA + DHA) reduced PMS symptoms in adolescents after 2 months
- Menstrual symptoms (pain) associated with low omega-3 fatty acid intake
- No benefit with general formulation of essential fatty acid
- Evening primrose oil (omega-6) not more beneficial than placebo

Treatment—Diet

- Low-fat, vegetarian diet beneficial for PMS symptoms
- Also increased concentration of sex hormone binding globulin (N = 33, diet for 2 cycles)

“Chocolate: Food or Drug?”

- 40% to 50% of women who crave sweets and chocolate do so primarily premenstrually
- Refractory to treatment!
  - Trial of progesterone vs alprazolam vs placebo; none helpful in decreasing cravings
  - Correct dietary deficiencies (eg, magnesium)
  - Increase levels of neurotransmitters
  - Biologically active compounds (methylxanthines, biogenic amines, cannabinoid-like fatty acids)

Treatment Strategies for PMDD, Premenstrual Mood Exacerbation

<table>
<thead>
<tr>
<th>Treatment</th>
<th>How to Add</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antidepressants</td>
<td>Monotherapy/intermittent or daily dosing; can increase dose premenstrually</td>
<td>Serotonergic antidepressants, SSRI's best studied</td>
</tr>
<tr>
<td>Oral contraceptives</td>
<td>Variable results; microtherapy or adjunctive therapy</td>
<td>Results vary between women and OCP preparation; watch for OCP dysphoria, contraindicated in smokers &gt; 30 years</td>
</tr>
<tr>
<td>Exercise</td>
<td>Adjunctive strategy</td>
<td>Overall improved nutrition, decrease saturated fat, increased fruit, vegetables</td>
</tr>
<tr>
<td>Nutrition—general, decrease fat</td>
<td>Adjunctive strategy</td>
<td>Overall improved nutrition, decrease saturated fat, increased fruit, vegetables</td>
</tr>
<tr>
<td>Omega-3 fatty acids</td>
<td>Adjunctive strategy</td>
<td>1 to 3 g EPA-DHA per day</td>
</tr>
<tr>
<td>Calcium</td>
<td>Adjunctive strategy</td>
<td>1200-1500 mg calcium per day</td>
</tr>
</tbody>
</table>

OCP = oral contraceptive pill.
Practical Take-Away Points

- PMDD is temporally related to the menstrual cycle
- Because individual symptoms may be non-specific to the diagnosis, assessment of the timing of symptoms is key in the diagnosis
- Women with mood or anxiety disorders may have markedly increased symptoms during the premenstrual phase, which is not technically PMDD
- Treatment choices include serotonergic antidepressants, oral contraceptives, mood tracking, and lifestyle changes

The Menopausal Transition

Perimenopause

- 2 to 8 years preceding menopause; may last 1 year after final menses
- Biological, hormonal, and clinical changes
  - Typically begin after age 40
- Hormonal assays are unreliable
- Risk of depression increased perimenopausally

Menopausal Status is Associated with Increased Depressive Symptoms

Menopausal status was significantly associated with incidence of higher depressive symptoms. Highest risk observed in transition phases.

Stages of Reproductive Aging Workshop (STRAW)

- Menopause: >12 months amenorrhea, reflects a complete but natural decrease in ovarian hormone secretion
- Menopausal transition: menstrual cycle and endocrine changes, begins with menstrual cycle changes, <12 months since last menses
- Postmenopause
- Early postmenopause: 5 years since last menses, further dampening of ovarian hormone function
- Perimenopause: “about or around the menopause,” includes menopausal transition, until 1 year past final menses

Risk of Core Menopause Symptoms

- Hot flashes
  - Affect 60% to 80%
- Sleep disorder
  - 2-fold increase vs premenopausal women
- Major depression
  - 2-fold increase vs premenopausal women


Risk of MDD in Perimenopause

- Risk for new onset of depression during the menopause transition: the Harvard study of moods and cycles and Penn Study
- Longitudinal, prospective studies; premenopausal women without histories of depression
- Over course of studies, women who entered the perimenopause were 2 to 4 times as likely to develop depression as those who remained premenopausal during the follow-up
- Increased hormonal variability associated with increased risk of depression

Sex Hormones and Perimenopausal Depression

- Role of sex hormones in perimenopausal MDD
  - Stages of the menopausal transition characterized by hormonal fluctuation, estradiol withdrawal most likely associated with MDD onset
  - Trials demonstrating antidepressant effects of estradiol, at least in short-term studies (3 to 6 weeks)
  - Experimentally induced estradiol withdrawal triggers mood symptoms in some women

Potential Mechanisms of Perimenopausal Depressive Symptoms

Complaints of fatigue, poor sleep
- Do you snore
- Suspect sleep apnea

Risk factors
- Age
- Obesity/BMI
- Smoking
- Menopause – an independent risk factor

Sleep and Fatigue

BMI = body mass index.


Hormone Replacement Therapy Study Halted

Increased risk of breast cancer a factor, government says

August 14, 2002 Posted: 11:56 AM EDT (1556 GMT)

WASHINGTON (CNN) -- In a move that may affect millions of women, U.S. government scientists Tuesday stopped a major study of hormone replacement therapy on the risks and benefits of combined estrogen and progestin in healthy menopausal women, citing an increased risk of invasive breast cancer.

Researchers from the National Heart, Lung and Blood Institute of the National Institutes of Health also found increases in coronary heart disease, stroke and pulmonary embolism.


Estrogen for Menopausal Depression: What is the Evidence?

- Systematic Review; only 5 RCTs with depressed participants; only 2 of the study samples were solely perimenopausal
- Difficult to generalize
  - Little evidence to support the use of estradiol to improve mood in nondepressed patients
  - Some evidence to support the antidepressant efficacy of estradiol in perimenopausal but not postmenopausal women

Serotonin Reuptake Inhibitors—Perimenopause

- Fluoxetine: Decrease in hot flashes
- Citalopram: Open-label for perimenopausal depression; monotherapy or as augmentation of estrogen
- Paroxetine: Decreases in hot flashes (FDA approval at low dose)
- Venlafaxine: Decrease in hot flashes; open-label for perimenopausal depression
- Mirtazapine: Open-label for perimenopausal depression
- Escitalopram: Open-label for perimenopausal depression
- Duloxetine: Open-label for perimenopausal depression

Hot Flashes: Integrative Treatments

- Placebo-controlled study assessing omega-3 fatty acids (ethyl EPA vs placebo) in the treatment of hot flashes in women who were experiencing "psychological distress" at baseline
- N = 120 women, age 40 to 55; randomized to EPA vs placebo for 8 weeks
  - All had hot flashes
  - After 8 weeks, hot flash frequency and score decreased significantly in the EPA group compared with placebo group
  - Menopause-Specific Quality of Life scores improved significantly over time in both groups
  - Measures of Psychological Distress: at baseline, women with psychological distress were mildly to moderately depressed; 24% met criteria for a major depressive episode
  - After 8 weeks, mood outcomes improved in both groups, but no significant differences on HAM-D scores for women with major depressive episodes (N = 29)

Ham-D = Hamilton Rating Scale for Depression.

Hot Flashes: Integrative Treatments

- MsFlash: National Institutes of Health funded multisite network, large study of exercise, yoga, and omega-3 fatty acids for hot flashes
  - 12-week study; N = 355 women with an average of 7.6 hot flashes per day
  - All randomized to either omega-3 or placebo
  - Also randomized to yoga, exercise, or usual activity
  - No efficacy for hot flashes with any intervention

Nonhormonal Treatments for Hot Flashes

<table>
<thead>
<tr>
<th>Agent</th>
<th>Indication</th>
<th>Study Designs, Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serotonergic antidepressants</td>
<td>Hot flashes, MDD</td>
<td>RCTs, open trials, with and without HRT; fluoxetine, paroxetine, citalopram, escitalopram, venlafaxine, desvenlafaxine, mirtazapine, duloxetine</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>Hot flashes</td>
<td>Randomized, double-blind, placebo-controlled trials showing benefit for hot flashes</td>
</tr>
<tr>
<td>Omega-3 fatty acids</td>
<td>Hot flashes</td>
<td>1 RCT showing benefit for hot flashes; not consistent across studies</td>
</tr>
<tr>
<td>Isoflavones/soy</td>
<td>Hot flashes</td>
<td>Randomized, double-blind, placebo-controlled trial; some positive and negative results</td>
</tr>
<tr>
<td>Black cohosh</td>
<td>Hot flashes</td>
<td>Several RCTs; no benefit over placebo</td>
</tr>
</tbody>
</table>

Treatment Strategies: Menopausal MDD and Hot Flashes

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Efficacy for Depression</th>
<th>Efficacy for Hot Flashes</th>
<th>Efficacy for Sleep</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antidepressant – serotonergic activity</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Hormone therapy</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Gabapentin</td>
<td>X</td>
<td>?</td>
<td></td>
</tr>
<tr>
<td>Sleep medication</td>
<td>X</td>
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Tamoxifen and Antidepressants

- Tamoxifen—a selective estrogen receptor modulator
- Active metabolites responsible for much of its anti-cancer cell proliferation properties
- Metabolized through cytochrome P450 2D6 (CYP2D6); CYP 3A4 and 3A5
- Efficacy appears related to polymorphisms for 2D6
- Medications that inhibit CYP2D6 can decrease concentrations of tamoxifen metabolites—risk of lowered efficacy, increased risk relapse of cancer
- Avoid concurrent use of fluoxetine, paroxetine, bupropion—strongest inhibitors of its metabolism

Question: What is the safest antidepressant to start for a patient with breast cancer remission on tamoxifen?

A. Venlafaxine
B. Bupropion
C. Paroxetine
D. Fluoxetine
E. Sertraline

Practical Take-Aways

- Women are vulnerable to depressive relapse or new onset during the menopausal transition
- Co-occurring symptoms of menopause are often important targets of treatment to be concurrently addressed
  - Hot flashes, sleep dysregulation, etc.
- Antidepressants are commonly used for menopausal symptoms, particularly as hormonal therapies have demonstrated greater risk and fewer long-term benefits as once believed

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