PMDD and Depression During the Menopausal Transition: New Insights

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Disclosures

Neither I nor my spouse/partner has a relevant financial relationship with a commercial interest to disclose.
Depression and Anxiety Across the Female Reproductive Cycle

- Premenstrual depression/anxiety (eg, PMDD)
- Depression/anxiety during pregnancy
- Depression/anxiety associated with infertility, miscarriage, or perinatal loss
- Depression/anxiety during the perimenopausal period
- Depression/anxiety during the postpartum period

- Menarche
- Pregnancy
- Menopause
Premenstrual Mood Changes

• The majority of reproductive age women report unpleasant symptoms around the time of menstruation.
  – Physical and psychological symptoms
  – “More emotional”
  – Minimal effect on functioning

Prevalence of Premenstrual Conditions

100% = all women of childbearing age.

PMS 75%
Nothing 20%
PMDD 5%
(3-8% of women of childbearing age)

Premenstrual Syndrome (PMS)

- Pattern of physical, emotional and behavioral symptoms occurring 1-2 weeks before menstruation
- Remit with the onset of menstruation
- 30-80% of women
- Significant in 3-8% of women
PMS Symptoms

- Psychological Symptoms
- Behavioral Symptoms
- Physical Symptoms
PMDD - DSM-V Criteria

- Criterion A: in most menstrual cycles during the past year, at least 5 of 11 symptoms (including at least 1 of the first 4 listed) were present:
  - Markedly depressed mood, hopelessness, or self-deprecating thoughts
  - Marked anxiety, tension, feelings of being “keyed up” or “on edge”
  - Marked affective lability
  - Persistent/marked anger or irritability or interpersonal conflicts
  - Decreased interest in usual activities
  - Subjective sense of difficulty in concentrating
  - Lethargy, easy fatigability, or marked lack of energy
  - Marked change in appetite, overeating, or specific food cravings
  - Hypersomnia or insomnia
  - A subjective sense of being overwhelmed or out of control
  - Other physical symptoms, such as breast tenderness or swelling, headaches, joint or muscle pain, a sensation of bloating, or weight gain
  - The symptoms must have been present for most of the time during the last week of the luteal phase, begun to remit within a few days of the onset of menstrual flow, and absent in the week after menses.
DSM-V Criteria

- Criterion B is that the symptoms must be severe enough to interfere significantly with social, occupational, sexual, or scholastic functioning.
- Criterion C is that the symptoms must be discretely related to the menstrual cycle and must not merely represent an exacerbation of the symptoms of another disorder, such as major depressive disorder, panic disorder, dysthymic disorder, or a personality disorder.
- Criterion D is that criteria A, B, and C must be confirmed by prospective daily ratings during at least 2 consecutive symptomatic menstrual cycles. The diagnosis may be made provisionally before this confirmation.
Premenstrual Exacerbation (PME)

- Mood disorders can worsen premenstrually
- PMDD vs. PME
- 40% of women screened for PMDD have an underlying mood disorder with PME
- Charting to determine cyclicity of symptoms

PMDD vs. Premenstrual Exacerbation (PME)

Symptom Severity

- PMDD
- PME

Menses | Ovulation | Menses

0 | 1 | 2 | 3 | 4

PME | PMDD
## Prospective Rating for Patient With PMS

### Premenstrual Daily Symptom Chart

**Name:** Jane Doe  
**Month:** September

1. Circle the days of your menstrual period in the row labeled Day of Month.
2. Begin your ratings today. For example, if today is the 12th day of the month, mark your symptoms in the column labeled 12. At the same time each day, use a marker or pen to fill in the correct numbered box to show how severe each symptom was over the past 24 hours. Leave the symptom blank if you had no problem with that symptom. See example on the right. If you forgot to fill in a day, place an X in the Day of Month box to signify that you did not fill in the chart for that day.
3. Continue on new page on the first day of the next month.

### Day of Month

| Day of Month | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25 | 26 | 27 | 28 | 29 | 30 | 31 |
| Irritability |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Sudden mood changes |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Tension |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Sadness |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Decreased interest in usual activities |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Feeling overwhelmed |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Difficulty concentrating |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Bloating |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Breast tenderness |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Food cravings |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Lack of energy |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Change in sleep |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Relationship problems |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
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## Premenstrual Daily Symptom Chart

**Name:** Jane Doe  
**Month:** March

1. Circle the days of your menstrual period in the row labeled Day of Month.
2. Begin your ratings today. For example, if today is the 12th day of the month, mark your symptoms in the column labeled 12. At the same time each day, use a marker or pen to fill in the correct numbered box to show how severe each symptom was over the past 24 hours. Leave the symptom blank if you had no problem with that symptom. See example on the right. If you forgot to fill in a day, place an X in the Day of Month bar to signify that you did not fill in the chart for that day.
3. Continue on new page on the first day of the next month.

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Prospective Rating for Patient With PMDD
Prospective Rating for Patient With Depression

Premenstrual Daily Symptom Chart

Name: Jane Doe
Month: July

1. Circle the days of your menstrual period in the row labeled Day of Month.
2. Begin your ratings today. For example, if today is the 12th day of the month, mark your symptoms in the column labeled 12. At the same time each day, use a marker or pen to fill in the correct numbered box to show how severe each symptom was over the past 24 hours. Leave the symptom blank if you had no problem with that symptom. See example on the right. If you forgot to fill in a day, place an X in the Day of Month box to signify that you did not fill in the chart for that day.
3. Continue on new page on the first day of the next month.

| Day of Month | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25 | 26 | 27 | 28 | 29 | 30 | 31 |
| Irritability|   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Sudden mood changes|   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Tension     |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Sadness     |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Decreased interest in usual activities|   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Feeling overwhelmed|   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Difficulty concentrating|   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Bloating    |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Breast tenderness|   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Food cravings|   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Lack of energy|   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Change in sleep|   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Relationship problems |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Other       |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Suicidal Thoughts |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |

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The Menstrual Cycle

Hormones
- LH
- Estrogen
- Progesterone
- FSH

Ovary
- Follicles
- Corpus luteum

Uterus

Days
- 1: Menses
- 5
- 14: Ovulation
- 28

FOLLICULAR

LUTEAL

Pathophysiology

- No clear evidence of “hormonal dysregulation”

- PMS/PMDD may represent an abnormal response to normal fluctuations of gonadal steroids

Hormonal Basis of PMDD

- Differential sensitivity to normal changes in estrogen and progesterone
- GnRH agonists are effective therapy
  - Eliminate hormonal fluctuation
  - PMS re-occurs with add-back therapy

GnRH = gonadotropin-releasing hormone.

Hormonal Basis of PMDD

Pathophysiology

ESTROGEN

PROGESTERONE

CENTRAL NEUROTRANSMISSION

SEROTONERGIC/NORADRENERGIC/DOPAMINERGIC

SEROTONIN TRANSMISSION ABNORMALITY

PMDD
Pathophysiology

Role of gamma amino-butyric acid (GABA)
Allopregnanolone enhances effects of GABA
-Metabolite of progesterone
-Positive modulator of GABA$_A$ receptor
Treatment with allopregnanolone antagonist during the luteal phase reduced PMDD scores on the DRSP.

PMS/PMDD Longitudinal Course

- Women seek treatment in their late 20s/early 30s
- Peaks around 30-39 years old\(^1\)
- Physical/mood symptoms stable from cycle to cycle\(^2\)
- Diagnosis appears stable over time\(^3\)
- **Chronic course**: symptoms may worsen over time [with age\(^4\), pregnancy\(^5\)]

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Risk Factors for PMDD and PMS

• Family history of PMS and PMDD\textsuperscript{1,2}
• History of postpartum depression\textsuperscript{3}
• Major depression past\textsuperscript{3,4} or future\textsuperscript{5}
• Mood changes induced by oral contraceptives

Pharmacologic Treatment

SSRIs are first line treatment
- Low dose
- Rapid response
- Fluoxetine, sertraline, and controlled release paroxetine are FDA approved

Antidepressants with serotonergic activity are also effective:
- clomipramine
- venlafaxine
- duloxetine

Antidepressant Dosing

- Continuous
  - Steady dose throughout the month
- Intermittent
  - Luteal phase
- Luteal phase increase
  - Continuous with luteal phase “bump up”
Who is a Candidate for Intermittent Treatment?

- Women who have premenstrual symptoms that require pharmacologic treatment
- Women without additional psychiatric co-morbidity that would require daily treatment
- Women with fairly regular menstrual cycles who can estimate when to initiate treatment
Duration of Treatment in PMDD

• Many women relapse when they stop treatment—as early as 1 to 2 cycles $^{1-5}$

• Well tolerated and efficacious when used longer than 6 months in open-label studies $^{1-3}$

• Patients should be reevaluated regularly
  – Chronic treatment may be necessary

Oral Contraceptives (OC) and PMS/PMDD

- Evidence from double-blind, randomized, placebo-controlled trials supports use of some OCs for treatment of PMDD.

- OCs containing drospirenone may be more effective.
  - derivative of spironolactone versus testosterone derived progestins
OCP Dosing

• Cyclic
  – 21 days active pill, 7 days placebo

• Continuous
  – Consecutive pill packs without a placebo
  – Efficacy greater than cyclic dosing

Consider: medical risks of OCP
OCP can increase suicide risk


Gonadotropin-Releasing Hormone Agonists for PMDD

- Leuprolide/buserelin
- Down-regulate gonadotrophin receptors in pituitary to create a hypogonadotrophic state
- Induce a reversible medical menopause
- Administered by nasal spray or subcutaneously
- Treatment usually restricted to six months

Gonadotropin-Releasing Hormone Agonists

- Side effects: hot flashes, vaginal dryness, osteoporosis

- Add-back estrogen and progesterone may reduce the effectiveness of the GnRH agonist treatment of PMS due to the induction of mood and anxiety symptoms
Gonadotropin-Releasing Hormone Agonists

• Double-Blind, placebo-controlled trials
  – Several show superiority of GnRH agonists over placebo\textsuperscript{1–8}
  – Some show GnRH agonists equal to placebo\textsuperscript{9,10}
  – Not first line

Non-Pharmacologic Treatment

- Mood Charting
- Lifestyle Modification
- Psychotherapy
- Nutritional Supplements
- CAM

Nutritional Supplements

- Calcium (1200 mg daily)
- Vitamin B6 (50-100 mg daily)
- Magnesium (200-460 mg daily)
- Vitamin E (400 IU daily)

Herbal Remedies

• Vitex Agnus Castus (Chasteberry)
  – Association of Reproductive Health Professionals includes VAC as a treatment option
  – Data are inconclusive
  – Potential benefits
  – Unclear mechanism: D2 receptor, estrogen receptor

• St. John’s Wort
  – Physical symptoms > emotional symptoms
  – 13-15% reduction in the level of OCP

Summary

- Premenstrual symptoms are common.
- A smaller percentage of women experience severe physical and emotional symptoms that interfere with their ability to function.
- Screening for these symptoms is important as it may lead to treatments that can be beneficial.
- Treatments can be non-pharmacologic or pharmacologic.
  - Hormonal or psychotropic
What is Menopause?

• 12 months without menses
• Menopausal transition—endocrinologic, somatic, psychological changes
• Average age is 51 (lower for smokers)
• Severity, frequency and variety of symptoms vary widely
• Perimenopause = passage from reproductive to non-reproductive life
MENOPAUSAL TRANSITION

What is Menopausal transition?

- **Menopausal transition**: from the first features of approaching menopause until up to 1 year after final menstrual period
- Associated with significant hormonal variability over time
- Overall, **decline in estrogen levels** over the menopausal transition

Longo et al. *Harrison’s Principles of Internal Medicine, 18th edition.*
Symptoms

• Hot flashes
• Vaginal dryness
• Depression/anxiety
• Osteopenia/osteoporosis
• Sleep changes
• Fatigue
• Concentration difficulty
Hot Flashes

Sensation of warmth of the upper body
Last 30 seconds – 5 minutes
Accompanied palpitations, anxiety, dizziness
May result in a cold sensation and/or chills
Daytime and/or night
Can occur from perimenopause through post menopause
45-85% of women
  Severe in 10-15% of women
Associated sleep disruption
Hot Flashes

• Natural menopause
  – Vasomotor symptoms decrease over a few years

• Surgical menopause
  – Severe vasomotor symptoms post-surgery
Depression-Risks

- History of depression
  - Women without lifetime MDD = lower risk of developing MDD during midlife vs women with prior MDD (28% v. 59%)
- History of postpartum depression
- Higher BMI
- Vasomotor symptoms
- Surgical menopause
- Estrogen itself may also have an antidepressant as well as a direct sleep effect

Depression

Meta-analysis of 14 observational studies
Lower likelihood of postmenopausal depression with longer duration of reproductive age
   – Age at menopause minus age at menarche

Premature menopause associated with higher rates of depression

Georgakis MK. JAMA Psychiatry. 2016;73:139-149.
Sleep

- Sleep disruption is the hallmark of menopause
- Nighttime vasomotor symptoms correlate with increased sleep fragmentation
  - Depression is more common in this group
- Sleep disordered breathing more common during menopause (weight gain, unknown endocrine reasons)
- Also increase in fibromyalgia and insomnia/depression
- Menopausal sleep disruption can exacerbate other conditions, i.e. circadian disorders and RLS


Treatment

- Hormone replacement therapy
- Antidepressants
- Other psychotropics
- Complementary and alternative medications
- Non-pharmacologic treatment
Hormone Replacement Therapy

• Gold standard until late 1990s
• Results from WHI changed practice
  – Higher rates of CVA, coronary artery disease, breast cancer
  – Worsening cognition
  – Benefit: colorectal cancer and endometrial cancer
  – Average age mid-60s
HRT and Depression

• Rates of depression double to triple in the menopausal transition compared to pre and late menopause

• Estrogen +/- progesterone may alleviate depression
  – Eliminate fluctuations in estrogen levels

HRT and Depression

• Estrogen replacement may be effective in preventing depression during the menopausal transition
• RTC of 172 perimenopausal and early postmenopausal women
• Transdermal estrogen + intermittent micronized progesterone vs. placebo
• Hormone therapy reduced the risk for depression by half

HRT and Mortality

- 27,000 postmenopausal women
- HRT with conjugated equine estrogen (CEE) plus medroxyprogesterone acetate (MPA) median of 5.6 years
- or with CEE alone for a median of 7.2 years
- No increased risk of all-cause, cardiovascular, or cancer mortality
  - Did not prevent CV disease, other chronic diseases, or reduce mortality

Antidepressants

• SSRIs/SNRIs – helpful
• Depression and vasomotor symptoms
  – Paroxetine is FDA approved for hot flashes
  – Fluoxetine, escitalopram, venlafaxine also helpful
Antidepressants and Fractures

- Antidepressants linked to bone loss in the past
- Women with higher anxiety levels had a greater number of fractures over 10 years
- 192 postmenopausal women, avg. age 68
- 20% of women with lowest anxiety levels had a fracture vs 25% of those with highest anxiety
  - Higher anxiety associated with lower bone mineral density in the lumbar spine and femoral neck

Other Psychotropics

- Gabapentin
  - Improvement in sleep and hot flashes
  - Dose 100-3600 mg
- Sleep meds
  - Zolpidem, eszopiclone improve sleep and hot flashes. 
    ? Low dose TCAs (e.g. doxepin)
- Clonidine
  - Improves hot flashes
- Armodafinil
  - Improves fatigue
CAM

• Black cohosh – limited data, mixed results
• Omega-3 – improvement in hot flashes
• Soy – mixed results; significant placebo response

Non-pharmacologic

- CBT
- Yoga
- Exercise
CBT-Meno
psychoeducation
cognitive behavioral strategies
  VMS
depressive symptoms
anxiety
sleep
sexual concerns
Improvement sustained at 3 months post-treatment

Sleep disturbance is a common among peri- and post-menopausal women. 7 interventions for sleep were assessed as part of MS-FLASH, RTCs for insomnia.

Yoga and Hot Flashes

- Meta-analysis, of 13 RTCs with a total of 1306 participants
- Improvements in psychological, somatic, vasomotor, and urogenital symptoms

Cramer H, Peng w, Lauche R. *Maturitas*, March 2018
Summary

• It is important to identify mood symptoms during the menopausal transition
• Menopausal symptoms other than mood (sleep, vasomotor) can significantly affect quality of life
• Symptoms are treatable with pharmacologic and non-pharmacologic interventions