Managing Depression in Women's Health
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Relevant Disclosures
none
Outline

- **Diagnosis/Screening**
  - Premenstrual Dysphoric Disorder
  - Non-pharmacological treatments
  - Antidepressants: Selection and Side Effect Management
  - Antidepressants in Pregnancy + Lactation
  - Osteoporosis, GI bleeding, QTc, and Suicide
  - Questions and Summary

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**Depression in Primary Care:**

2 Simple Screening Questions:
- “During the past 2 weeks, have you felt down, depressed or hopeless?”
- “During the past 2 weeks, have you felt little interest or pleasure in doing things?”

*The US Preventive Services Task Force*

*JAMA, June 18, 2003- Vol 289 (23)*
The Three S’s of the Psychiatric Interview

1) S – Stressors/triggers
2) S – Suicidality
3) S – Substance Abuse

Diagnosis of Depression
Key issues

1) Rule out Medical conditions causing psychiatric symptoms
2) Rule out Substance abuse or iatrogenic medications
3) Rule out Bipolar disorder (ie, screen for mania or hypomania)
Physical Health Questionnaire-9, depression scale

- Nine (9) items
- Easy to score
- There are two components of the PHQ-9:
  - Diagnostic
  - Severity
- See handout or Google: “PHQ-9”

http://www.depression-primarycare.org/clinicians/toolkits/materials/forms/phq9/
Case Vignette

Three weeks ago, a 59yo Caucasian woman with a history of CHF, depression, and alcohol abuse presents to your office with three months of depressed mood. At that time, you started her on citalopram 20mg at bedtime.
She has been on hydrochlorothiazide and potassium supplements for over one year.

Case Vignette

Today in your office, she describes improved energy but significantly worsened irritability and insomnia, with new onset hyperactivity, racing thoughts, and impulsivity. She also endorses ruminative suicidal thoughts.
Case Vignette
Question
Which ONE of the following interventions is MOST appropriate?
   a. Initiation of divalproex 500mg qhs
   b. Increase citalopram to 40mg daily
   c. Stop citalopram
   d. Trial of quetiapine 50mg daily
   e. Urine toxicology screen

Case Vignette
Answers Discussed
   a. Divalproex is the preferred treatment for bipolar disorder in patients with potential electrolyte and fluid shifts.
   b. If this patient is having a mixed episode, antidepressants may be the cause and are therefore contraindicated.
   c. Stopping citalopram is probably the most appropriate intervention.
   d. Low-dose atypical antipsychotics can target insomnia, racing thoughts, and agitation.
   e. Urine toxicology screen is indicated to rule out substance abuse.
Antidepressants are generally contraindicated in bipolar disorder

• Generally have NOT been shown to be effective in bipolar depression
• May trigger mania or hypomania
• May trigger rapid cycling or mixed episode

Mood Disorders Questionnaire

• Self-administered, one-page questionnaire
  (see attached at end of syllabus)
• 7 or more positive responses is a positive screen


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Women and Depression

- More likely to present with atypical symptoms and anxiety
- More likely to respond to SSRIs (higher plasma levels of sertraline)
- Less likely to respond to TCAs (more likely to experience ADRs to TCAs)


Premenstrual dysphoric disorder or MDD?
Disorders with Premenstrual Exacerbation (PME)

- Affective disorders
- Anxiety disorders
- Psychotic disorders
- Eating disorders
- Personality disorders
- Substance abuse
- Migraine
- Allergies
- Asthma
- Seizures

Menstrual Cycle Week and All Psychiatric Admissions

If random, admissions of women to psychiatric hospitals for all psychiatric diagnoses would be 25% on each week of the menstrual cycle.

Menstrual Cycle


PMDD vs Normal PMS

**Normal PMS (Premenstrual Syndrome):**
- 80% of women
- Mild to moderate emotional fluctuations

**PMDD (Premenstrual Dysphoric Disorder):**
- 3-8% of women
- Severe moods swings, depressed mood, irritability

DSM-IV Research Criteria For PMDD

A. In most menstrual cycles during the past year, **five (or more) of the following symptoms** were present for most of the time during the last week of the luteal phase, began to remit within a few days after the onset of the follicular phase, and were absent in the week postmenses, with at least one of the symptoms being either (1), (2), (3), or (4):

“Depression NOS”

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DSM-IV Research Criteria For PMDD

A. [Continued]

1. Markedly depressed mood, feelings of hopelessness, or self-deprecating thoughts
2. Marked anxiety, tension, feelings of being "keyed up" or "on edge"
3. Marked affective lability (e.g., feeling suddenly sad or tearful)
4. Persistent and marked anger or irritability or increased interpersonal conflicts
5. Decreased interest in usual activities (e.g., work, school, friends, hobbies)
6. Subjective sense of difficulty in concentrating
7. Lethargy, easy fatigability, or marked lack of energy
8. Marked change in appetite, overeating, or specific food cravings
9. Hypersomnia or insomnia
10. A subjective sense of being overwhelmed or out of control
11. Other physical symptoms, such as breast tenderness or swelling, headaches, joint or muscle pain, a sensation of "bloating," or weight gain
DSM-IV Research Criteria For PMDD

B. The disturbance markedly interferes with work or school or with usual social activities and relationships with others.

C. The disturbance is not merely an exacerbation of the symptoms of another disorder (although it may be superimposed on any of these disorders).

D. Criteria A, B, and C must be confirmed by prospective daily ratings during at least two consecutive symptomatic cycles.

Daily Record of Symptoms

| Symptom | 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 |
|---------|---|---|---|---|---|---|---|---|---|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|
|         |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |

Circle the dates of your period.

Mild [ ]
Moderate [ ]
Severe [ ]
Menstrual Cycle

Mechanism of PMDD?

1. Serotonin and hormones?
2. Falling progesterone?

Progestosterone → Allopregnanolone

Premenstrual Dysphoric Disorder Treatments

Two Main Treatments

• SSRI’s
• Hormones

All Possible PMDD Treatments

Antidepressants
- SSRI*
- SNRI*
Clomipramine**

Ovulation Suppression
OCPs*
GnRH Agonists (Lupron)**
Danazol (inhibits LH/FSH)
Oophorectomy

Anxiolytics
Benzodiazepines**
Buspar**

Other
Exercise
Calcium**
CBT*
Chasteberry
(Vit B6)
(NSAIDS)
(Diet)
(may reduce FSH or Prolactin)
Advantages of SSRI’s

- Fluoxetine, Sertraline and Paroxetine CR are FDA approved for PMDD
- Both continuous and intermittent dosing effective
- Intermittent Fluoxetine is effective for mood symptoms at both 10 and 20 mg. 20 mg is more effective for physical symptoms than 10 mg.*
- No discontinuation symptoms with intermittent dosing
- Dosing strategies can be tailored to a woman’s preferences


- Teri Pearlstein, M.D. Warren Alpert Medical School of Brown University, APA Conference 2008

Intermittent Fluoxetine in PMDD

![Graph showing the mean change from baseline for DRSP Mood Cluster, DRSP Physical Cluster, and DRSP Social And Functional Impairment Cluster for Placebo, Fluoxetine 10 mg, and Fluoxetine 20 mg.]

DRSP = Daily Record of Severity of Problems
What about hormone therapy?

Lower progestin potency:

- Ortho Evra patch
- Ovcon 35
- Ortho-TriCyclen
- Othro-Cyclen
- Brevicon
- Modicon

- Necon 1/35
- Alesse
- Levlite
- Tri-Levlen
- Triphasil
- Trivora


Which hormones are good for mood?

- Women are sensitive to hormones in different ways – some to the progestin, some to the amount and some to the hormonal fluctuation
- Seasonale or any monophasic OCP taken continuously can stabilize mood
- Women who are sensitive to hormonal fluctuation should avoid triphasic OCP’s
- It takes about 2 cycles to see if a certain OCP will work
PMDD References


Freeman et al. *An overview of four studies of a continuous oral contraceptive (levonorgestrel 90 mcg/ethinyl estradiol 20 mcg) on premenstrual dysphoric disorder and premenstrual syndrome.* Contraception 2012 May;85(5):437-45.


PMDD In Summary

- PMDD: 3-8% of women
- The current hypothesis: women who experience PMDD are sensitive to the change in estrogen and progesterone
- SSRIs are effective treatments with daily or luteal phase dosing—higher doses may be more effective for physical symptoms
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Other options

- Psychotherapy
- Bibliotherapy
- Self-help organizations
- Exercise
- Light therapy
- Complementary/alternative medications
### Bibliotherapy

- **Feeling Good**, by David Burns
- **Mind Over Mood**, by Greenberger and Padesky

### Self Help Organizations

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<tr>
<th>General Resources</th>
<th>National Mental Health Association (NAMH)</th>
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<tr>
<td></td>
<td>1821 Prince Street</td>
</tr>
<tr>
<td></td>
<td>Arlington, VA, 22201</td>
</tr>
<tr>
<td></td>
<td>Phone (703) 524-7800</td>
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<td>NAMI Helpline (800) 950-NAMI (6264)</td>
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<td>Colonial Place Three</td>
<td>1821 Prince Street</td>
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<tr>
<td>2107 Wilson Blvd, Suite 300</td>
<td>Alexandria, VA, 22314-2871</td>
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<tr>
<td>Arlington, VA, 22201</td>
<td>Phone (703) 524-7772</td>
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<td>Phone (703) 524-7800</td>
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<td>NAMI Helpline (800) 950-NAMI (6264)</td>
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<td></td>
</tr>
<tr>
<td>1401 H St. NW</td>
<td></td>
</tr>
<tr>
<td>Washington, DC, 20000</td>
<td></td>
</tr>
<tr>
<td>e-mail: <a href="mailto:namiworkplace@nami.org">namiworkplace@nami.org</a></td>
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<th>Depression and Bipolar Support Alliance (DBSA)</th>
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<td>formerly known as National Depressive and Manic Depressive Association (NMDA)</td>
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<tr>
<td>Child and Adolescent Bipolar Foundation (CABF)</td>
<td>730 North Franklin Street, Suite 501</td>
</tr>
<tr>
<td>1187 Wilmette Avenue P.M.B. #331</td>
<td>Chicago, IL, 60610-7204</td>
</tr>
<tr>
<td>Wilmette, IL, 60091</td>
<td>Phone (866) 820-5653</td>
</tr>
<tr>
<td>Phone (630) 264-0525 or (630) 403-0473</td>
<td>Website <a href="http://www.dbsa.org">www.dbsa.org</a></td>
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<th>Unwanted Co-Travelers</th>
<th>National Eating Disorders Association (NEDA)</th>
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<tr>
<td>Anxiety Disorders Association of America (ADAA)</td>
<td>501 Stewart Street, Suite 303</td>
</tr>
<tr>
<td>8770 Georgia Avenue Suite 800</td>
<td>Seattle, WA, 98103</td>
</tr>
<tr>
<td>Silver Spring, MD, 20910</td>
<td>Phone: 206-332-5857</td>
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<tr>
<td>Phone (301) 455-1001</td>
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On-line Psychotherapy for Depression

• **Depression Management Project**
  Google: “Depression Management Project”

• **MoodGym**

• **Beating the Blues**
  [http://www.beatingtheblues.co.uk/](http://www.beatingtheblues.co.uk/)

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• Diagnosis/Screening
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Antidepressant Overview

- Selective Serotonin Reuptake Inhibitors (SSRIs)
- “Other” Antidepressants: bupropion, duloxetine, mirtazapine, nefazadone, trazodone, venlafaxine
- Tricyclics (TCAs)
- Monoamine oxidase inhibitors (MAOIs)

How to pick antidepressant?
“Current evidence does not warrant the choice of one … antidepressant over another on the basis of differences in efficacy and effectiveness.”

“Other differences with respect to onset of action and adverse events may be relevant for the choice of a medication.”


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*Choosing an Antidepressant is Not Based on Efficacy?*

“Clinically important differences exist ...for both efficacy and acceptability in favour of escitalopram and sertraline.

Sertraline might be the best choice...”

Do No Harm

**SSRI’s and SGA’s**

Safer than:
Tricyclics
MAOI’s

---

**How to pick antidepressant?**

- Patient preference
- Patient or Family history of response
- Clinician familiarity
- Comorbidities—**Side effect profile**
The person who takes medicine must recover twice, once from the disease and once from the medicine.

Attributed to William Osler, MD

The Maze of Mood Medications

How do you choose?

Food
- Fast
- Good
- Cheap

Meds
- Sedation
- Sexual dysfunction
- Weight gain
- (Cheap)
Of 401 out-patients taking SSRIs:

<table>
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<tr>
<th>Most Common</th>
<th>Most Bothersome</th>
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<tbody>
<tr>
<td>drowsiness (38%)</td>
<td>drowsiness (17%)</td>
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<tr>
<td>dry mouth (34%)</td>
<td>sexual dysfunction (17%)</td>
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<tr>
<td>sexual dysfunction (34%)</td>
<td>weight gain (11%)</td>
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Choosing an Antidepressant Side Effects

- *Sedation/activation*
- Sexual dysfunction
- Weight gain
- (Cost)
Case Vignette

No medical problems
Depressed for 2 months

**Hypersomnia**

**Insomnia or anxious**

---

Relative activation vs. Sedation modern antidepressants

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<tr>
<th>Activating</th>
<th>Psychostimulants</th>
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<tr>
<td></td>
<td>Bupropion</td>
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<tr>
<td></td>
<td>Fluoxetine, Sertraline</td>
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<td>Venlafaxine, Escitalopram</td>
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<td></td>
<td>Citalopram</td>
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<td>Mildly to Moderately Sedating</td>
<td>Paroxetine, Fluvoxamine</td>
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<td></td>
<td>Nefazodone</td>
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<tr>
<td>Strongly sedating</td>
<td>Trazadone</td>
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<tr>
<td></td>
<td>Mirtazapine</td>
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Sedation Management Strategies

- Review other meds
- Switch from am to hs dosing
- Reduce dosage
- Switch to another AD
- ?Consider psychostimulant: methylphenidate or dextroamphetamine or modafinil

*(this is off-label)*


Choosing an Antidepressant Side Effects

- Sedation/activation
- *Sexual dysfunction*
- Weight gain
- (Cost)
Case Vignette

No medical problems
Depressed for 2 months

**Fears loss of libido**

Sexual dysfunction is common

- Women: 43% total, 22% low libido, 14% sexual arousal problems, 7% pain
- Men: 31% total, 21% premature ejaculation, 5% erectile dysfunction, 5% low libido

Remember to ask about sexual functioning beforehand

SEXUAL DYSFUNCTION

Effect on sexual functioning

<table>
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<th>Increased?</th>
<th>Psychostimulants</th>
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Sexual Dysfunction Strategies

Dose reduction

Timing of sexual activity

“Drug holiday”

Anti-dote therapy: (off-label)

anti-dote therapy: (off-label)
buspirone 45mg qd
dopamine (DA) agonists: amantadine
bupropion 300mg qd
$\alpha_2$-adrenergic receptor antagonists: yohimbine
psychostimulants: methylphenidate 5-20mg
PDE-5 inhibitors: Sildenafil 50-100mg qd
Choosing an Antidepressant
Side Effects

• Sedation/activation
• Sexual dysfunction
• **Weight gain**
• (Cost)

Case Vignette

No medical problems
Depressed for 2 months
**Obesity**

**Weight loss**
## Impact on weight

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<th>Weight loss (?)</th>
<th>psychostimulants</th>
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<td>Mild to moderate</td>
<td>SSri’s (fluoxetine &lt; paroxetine)</td>
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<td>Significant</td>
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## Weight Management strategies
Sample Year End Diary Entry

Alcohol units 3836 (poor)
Cigarettes 5277
Calories 11,090,265 (repulsive)

... 
Weight gained 74 lbs.
Weight lost 72 lbs (excellent)


Weight Management strategies

“Life style interventions”:
Eat healthy, exercise more
Get the right amount of sleep and reduce stress*
Address dry mouth
Switch or add bupropion
Add psychostimulants

Weight Management strategies

No sugared beverages
Increase fiber intake
Wait 20 minutes before second helping
1:1 “pay” for screen time with physical activity

Youtube -- “Sugar: The Bitter Truth”
90 minute video of talk given by Robert H. Lustig, MD, UCSF Professor of Pediatrics

Weight Management strategies (Off-Label)

- **Sibutramine** (Meridia): removed from US market b/o CV risks
- **Orlistat** (Xenical): 120mg tid w meals
- **Bupropion + Naltrexone** (Contrave): also rejected b/o increased P and BP (N16mg+B200mg BID)
- **Metformin**, studied in patients on atypical antipsychotics
- **Topiramate** 100-150mg daily
Choosing an Antidepressant
Side Effects

• Sedation/activation
• Sexual dysfunction
• Weight gain
• Cost

Case Vignette

No medical problems
Depressed for 2 months

No money
Cost of some psychiatric meds

<table>
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<td>Wellbutrin SR 150MG Tab</td>
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<td>Clonazepam 2mg tab</td>
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<td>Citalopram Hydrobromide 20mg Tab</td>
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<td>Diazepam 5mg tab</td>
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from Drugstore.com 7/16/11, prices subject to change, about 50% cheaper than local drugstore
*Descartes Li – Best Buy!

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Antidepressants in Pregnancy

- 2.3% (ca. 100K) out of 4 million infants born in the U.S. are exposed to SSRIs
- 30% of these discontinue ssri before second month of pregnancy
- 14.6% of pregnant women have diagnosis of substance abuse disorder
- Half of pregnancies in US are unplanned

Antidepressants in Pregnancy

- Baseline risk for birth defects is around 3%
- No randomized, controlled studies
- Not able to control for effects of depression during pregnancy
- Most studies indicate that SSRIs are associated with a small absolute risk, if any, for major defects
Depression Relapse in Pregnancy: Cohen et al. 2006:

- 43% of the women experienced relapse during pregnancy
- 26% who maintained medication relapsed
- 68% who discontinued medication relapsed


?pregnancy + currently on ADs

Is the patient acutely suicidal or psychotic?

No

Yes

Does the patient have moderate to severe symptoms?

No

Yes

Aggressively treat depression, consider a reasonable period of stability to attempt to conceive

Consider a reasonable period of stability before attempting to conceive

Did the patient start her antidepressant treatment less than 6 months ago?

No

Yes

Patient recently responded; consider a reasonable period of stability before attempting to conceive

Did the patient have recurrent episodes of MDD?

No

Yes

Unlikely there is strong evidence that psychotherapy alone would be ineffective, or the patient feels she needs to continue medication, she is eligible for trial off medication

Consider a period of normalcy, non-psychiatric clinicians should consider consultation with a psychiatrist to determine if a trial of psychotherapy alone is reasonable

Consider continuation of medication unless the patient feels that she would feel better to discontinue medication

Considering pregnancy, taking ADs

- Consider delay conceiving until stable
- If in full remission, but h/o both recurrence and non-response to psychotherapy, continue meds
- If in full remission with no h/o recurrence and/or non-response to psychotherapy, consider taper off medication and refer for therapy


Pregnant, depressed, not taking ADs

- If depression is severe, start meds
- If depression is not severe, and:
  - If pt has never failed a course of therapy, do therapy
  - If pt has failed therapy, start meds

Pregnant, depressed, taking ADs

- If depression is severe or therapy has been ineffective, continue and optimize meds
- If depression is not severe, and pt has either responded to therapy before or has never had therapy, start therapy either in combination with meds or (if symptoms are relatively mild) with a med taper


Which antidepressant is best in pregnancy?
Paxil and Cardiac Defects?

This meta-analysis found little evidence of publication bias or overall statistical heterogeneity and only weak evidence of associations with some study characteristics.


Antidepressants in Pregnancy

- Beware of using newer or less well studied ADs just because of lack of data
- Recommend monotherapy with lowest possible dose
- Consultations can be very useful
- See also www.motherisk.org

Antidepressants in Breastfeeding

- **Sertraline - 1st line**
  - Less than 10% maternal level
- **Fluoxetine**
  - Exceeded 10% maternal level (22% cases)
- **Citalopram**
  - Exceeded 10% maternal level (17% cases)
- **Escitalopram and Fluvoxamine**
  - Few case reports

Tricyclics, Heterocyclics, and Lactation

- **Nortriptyline** - undetectable in infant serum
  - Growing evidence that other tricyclics appear to be safe
- **Doxepin - cautioned** due to hypotonia, poor feeding
- **Mirtazapine** - no adverse effects reported
- **Bupropion**
- **SNRIs**
- **Trazodone** - infant levels less than 10%
- **MAOI inhibitors** - discontinue


Outline

• Diagnosis/Screening
• Premenstrual Dysphoric Disorder
• Non-pharmacological treatments
• Antidepressants: Selection and Side Effect Management
• Antidepressants in Pregnancy + Lactation
• **Osteoporosis, GI bleeding, QTc, and Suicide**
• Questions and Summary

GI Bleeding
SSRIs and GI bleeding

- Two potential mechanisms: platelet aggregation, gastric acidity
- Overall risk is low: 1 per 8000 SSRI prescriptions
- Associated also with increased blood loss during surgical procedures.
- TCAs, mirtazapine, and bupropion NOT associated with bleeding

What’s the bottom line?
You should mention this risk in the following situations:
- history of stomach ulcers or bleeding disorders.
- about to have surgery (consider stopping SSRI a few days in advance).
- taking NSAIDs, aspirin, warfarin, or antiplatelet drugs (clopidogrel).
SSRIs and osteoporosis

Two observational studies in *Archives of Internal Medicine*:

Women on SSRIs lost double the bone density of those either on tricyclics or on no antidepressants (2-year)

Men on SSRIs had 4-6% lower bone density than men on no antidepressants (cross-sectional)

Diem SJ et al., 2007;167(12):1240-1245.
Haney EM et al. 2007;167(12):1246-1251.
SSRIs and osteoporosis

More recent study, with longer follow-up, found association with:

• wrist fracture (HR = 1.30, 95% CI 1.04–1.62),
• but not with first hip fracture (HR = 1.01, 95% CI 0.71–1.44)


The bottom line

Warn your elderly patients about osteoporosis, even though the findings are still preliminary.
trial of 119 adults showed that QTc is increased in a dose-dependent fashion with citalopram


<table>
<thead>
<tr>
<th>Dosage</th>
<th>QT prolongation</th>
<th>CI (msec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20mg</td>
<td>8.5msec</td>
<td>6.2-10.8</td>
</tr>
<tr>
<td>60mg</td>
<td>18.5msec</td>
<td>16.0-21.0</td>
</tr>
<tr>
<td>40mg</td>
<td>12.6msec</td>
<td>inferred</td>
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</tbody>
</table>
Bottom Line

- Check EKG before you go higher than 40mg, then again after they have been on a higher dose
- If they're already on a higher dose, just check the EKG
- If QTc in men over 450 and women over 500, consider decreasing dosage or switching to escitalopram
- Review other risk factors for increased QTc

Antidepressants and Suicide Risk
Suicide Risk and Antidepressants

- In 2004, FDA issued a black box warning for children and adolescents warning of a risk of suicidal events.
- In 2007, another black box warning issued for adults up to 25 years of age. (based on an odds ratio, 1.55; 95% confidence interval, 0.91 to 2.70)


Suicide Risk and Antidepressants

Furthermore, benefit of antidepressants in pediatric patients is controversial

Suicide Risk and Antidepressants

Increase in suicidal ideation in children up to age 18, but not actual suicide. Probably suicide neutral or slightly beneficial in 25-65 yr age range

Hammad et al. Suicidality in pediatric patients treated with antidepressant drugs. *Arch Gen Psychiatry* 2006;63:332-339.


**Odds Ratios for Suicidal Behavior and Ideation among Patients Treated with Antidepressants for Psychiatric Indications, as Compared with Placebo.**

Data are from the Summary Comments of the December 13, 2006, meeting of the FDA's Psychopharmacologic Drugs Advisory Committee. CI denotes confidence interval.
Bottom line

- In younger patients (<25 years), suicide risk is increased
- Risk decreases with increasing age
- Warn younger patients (and their families) to monitor for increased suicidality

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