Handout for the Neuroscience Education Institute (NEI) online activity:

Mother May I? Managing Mental Illness During Pregnancy: Focus on Antidepressants
Learning Objectives

• Evaluate the potential risks of using antidepressants during pregnancy and postpartum

• Compare the risk–benefit analyses of specific antidepressants for the developing fetus and the breastfeeding infant

• Identify risk factors for the emergence of depressive symptoms during pregnancy and postpartum
The labels for antidepressants (SSRIs in particular) include several warning statements about possible adverse effects of use during pregnancy. Which of the following has the most evidence suggesting an increased risk with antidepressant use during pregnancy?

A. First trimester cardiac malformations
B. Persistent pulmonary hypertension of the newborn (PPHN)
C. Postnatal adaptation syndrome (PNAS)
D. Long-term neurodevelopmental abnormalities
Major Depression During Pregnancy and Postpartum

Period Prevalence

Conception to birth
Birth to 3 months postpartum

Incidence

ANTIDEPRESSANT USE DURING PREGNANCY
### FDA Use-in-Pregnancy Ratings

<table>
<thead>
<tr>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>X</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Controlled studies show no risk</strong></td>
<td><strong>No evidence of risk in humans</strong></td>
<td><strong>Risk cannot be ruled out</strong></td>
<td><strong>Positive evidence of risk</strong></td>
<td><strong>Contra-indicated</strong></td>
</tr>
</tbody>
</table>

#### What They Really Mean

<table>
<thead>
<tr>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>X</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>OK to use</strong></td>
<td><strong>I don't know</strong></td>
<td><strong>I don't know</strong></td>
<td><strong>I don't know</strong></td>
<td><strong>Contra-indicated</strong></td>
</tr>
</tbody>
</table>

#### # of Psychotropics With Rating

<table>
<thead>
<tr>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>X</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>0</strong></td>
<td><strong>8</strong></td>
<td><strong>66</strong></td>
<td><strong>16</strong></td>
<td><strong>6</strong></td>
</tr>
</tbody>
</table>

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Antidepressant Use During Pregnancy Has Been Associated With:

First Trimester

- Cardiac defect
- Minor physical malformation
- Major physical malformation
- Miscarriage

First Trimester

• 3% of infants in the US are born with a major birth defect

• Each specific type of major birth defect is rare

• Risk of congenital heart defects in general population is 0.82 per 1000 births

• Why might antidepressants increase the risk of some birth defects?
  – Serotonin is important during early embryonic development of the neural tube, branchial arches, and heart

Paroxetine Warning in FDA Label

Epidemiological studies have shown that infants exposed to paroxetine in the first trimester of pregnancy have an increased risk of congenital malformations, particularly cardiovascular malformations.
## Weighing the Evidence for First Trimester Teratogenicity: Studies

<table>
<thead>
<tr>
<th>Medication</th>
<th>Increased Risk (# Studies)</th>
<th>No Increased Risk (# Studies)</th>
</tr>
</thead>
<tbody>
<tr>
<td>bupropion</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>citalopram</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>duloxetine</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>escitalopram</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>fluoxetine</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>fluvoxamine</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>mirtazapine</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>paroxetine</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>sertraline</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>trazodone</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>venlafaxine</td>
<td>1</td>
<td>3</td>
</tr>
</tbody>
</table>

Varying methodology across studies. Causality and magnitude of risk unclear.

## Weighing the Evidence for First Trimester Teratogenicity: Meta-analyses

<table>
<thead>
<tr>
<th></th>
<th># Meta-analyses Finding Increased Risk</th>
<th># Meta-analyses Finding No Increased Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Major</td>
<td>Cardiac</td>
</tr>
<tr>
<td>citalopram</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>fluoxetine</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>paroxetine</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>sertraline</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>SSRI (class)</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Newer AD (class)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>AD (class)</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

Increased Risk of Major Malformations With Antidepressants: Summary

- **Paroxetine**
  - Increased risk of major and cardiac malformations in several studies
  - Not seen in large database assessments

- **Bupropion**
  - Limited data; possible increased risk of congenital heart defects

- **SSRIs**
  - Findings are inconsistently observed

- **Other newer antidepressants**
  - Very limited data

Antidepressant Use During Pregnancy Has Been Associated With:

- Persistent pulmonary hypertension
- Postnatal adaptation syndrome
- Preterm birth
- Low birth weight
- Small for gestational age
- Long-term neurodevelopmental effects?

Persistent Pulmonary Hypertension of the Newborn (PPHN)

- At birth, the lung replaces the placenta as the primary site of gas change
- → rapid drop in pulmonary vascular resistance and thus an increase in pulmonary blood flow
- PPHN can occur when this cardiopulmonary transition does not occur (1–2 cases per 1000 births)
- Presents within 12 hours of birth as cyanosis and mild respiratory distress
- Can progress to respiratory failure, requiring intubation and mechanical ventilation; fatal in 10–20% of cases

FDA Class Statement: PPHN

- Infants exposed to SSRIs in pregnancy may have an increased risk of persistent pulmonary hypertension of the newborn (PPHN); PPHN occurs in 1–2 per 1000 live births in the general population and is associated with substantial neonatal morbidity and mortality.

- Several recent epidemiological studies suggest a positive statistical association between SSRI use in pregnancy and PPHN.

- Other studies do not show a significant statistical association.
### Weighing the Evidence for Increased Risk of PPHN

<table>
<thead>
<tr>
<th></th>
<th># Studies Showing Increased Risk of Exposure</th>
<th># Studies Not Showing Increased Risk of Exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Early</td>
<td>Late</td>
</tr>
<tr>
<td>fluoxetine</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>SSRI</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>antidepressant</td>
<td>1</td>
<td>3</td>
</tr>
</tbody>
</table>

Varying methodologies. Studies did not assess duration of exposure. Most studies were underpowered.

Increased Risk of PPHN With SSRIs: Summary

- Unclear if SSRIs are linked to an increased risk of PPHN
- Possible that any risk is indirect via increased risk of preterm birth
- If there is an increased risk, what does that mean?
**PPHN and Antidepressants: Understanding the Risk**

**Study With Highest Relative Risk With AD Use**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Definite PPHN (N=377)</th>
<th>Matched Control (N=836)</th>
<th>Adjusted Odds Ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No AD during pregnancy</td>
<td>357 (94.7%)</td>
<td>799 (95.6%)</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>AD before wk 20</td>
<td>6 (1.6%)</td>
<td>26 (3.1%)</td>
<td>0.6 (0.2–1.5)</td>
<td>0.28</td>
</tr>
<tr>
<td>AD after wk 20</td>
<td>14 (3.7%)</td>
<td>11 (1.3%)</td>
<td>3.2 (1.3–7.4)</td>
<td>0.008</td>
</tr>
<tr>
<td>No SSRI during pregnancy</td>
<td>361 (95.8%)</td>
<td>812 (97.1%)</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>SSRI before wk 20</td>
<td>2 (0.5%)</td>
<td>18 (2.2%)</td>
<td>0.3 (0.1–1.2)</td>
<td>0.08</td>
</tr>
<tr>
<td>SSRI after wk 20</td>
<td>14 (3.7%)</td>
<td>6 (0.7%)</td>
<td>6.1 (2.2–16.8)</td>
<td>0.001</td>
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## PPHN and Antidepressants: Understanding the Risk

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<td>6 (0.7%)</td>
<td>6.1 (2.2–16.8)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

### What does the relative risk mean?

- **Population risk:**
  - 1–2 per 1000
- **Absolute risk w/ SSRI:**
  - 6–12 per 1000

**In other words:**

- Rate of no PPHN in population: ~99%
- Rate of no PPHN w/ SSRI: ~99%

Postnatal Adaptation Syndrome (PNAS)

- 20–30% of infants exposed to SSRIs in late pregnancy exhibit symptoms such as irritability, abnormal crying, tremor, lethargy, hypoactivity, decreased feeding, tachypnea, and respiratory distress
- Termed PNAS; also called neonatal behavioral syndrome or poor neonatal adaptation syndrome
- Usually develops within days of birth and resolves within days or weeks

FDA Class Statement: Postnatal Adaptation Syndrome

- Neonates exposed to SSRIs or SNRIs late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding; such complications can arise immediately upon delivery.

- Reported clinical findings have included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying.

- These features are consistent with either a direct toxic effect of SSRIs and SNRIs or possibly a drug discontinuation syndrome.
Weighing the Evidence for Risk of PNAS

<table>
<thead>
<tr>
<th># Studies Showing Increased Risk of Exposure</th>
<th># Studies Not Showing Increased Risk of Exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>4</td>
</tr>
</tbody>
</table>

• Some conflicting evidence
  – Varying methodologies

• Overall, data suggest that PNAS can occur in neonates exposed to SSRIs or SNRIs

• Most often reported after exposure to paroxetine, fluoxetine, or venlafaxine

PNAS: Why and How It May Occur

- All SSRIs cross the placenta and thus may increase serotonin in the developing fetus

- Suggested causes of PNAS
  - Serotonin toxicity (symptoms resemble serotonin syndrome)
  - Discontinuation syndrome (symptoms resemble adult serotonin discontinuation syndrome)

- Severity and duration of PNAS are affected by:
  - Antidepressant dose, timing, duration of exposure, and pharmacokinetics
  - Genetic predisposition?
Long-term Neurodevelopmental Outcomes

• Very limited data
• No studies found detrimental effects on cognitive development
• Two studies found possible effects on motor development
• Studies that exist are reassuring but have limitations
  – Most did not follow children through school-age
  – Most did not control for maternal IQ
  – Most did not measure maternal treatment adherence

FDA Class Statement: AD Discontinuation and Depression Relapse

• Physicians should also note the results of a prospective longitudinal study of 201 pregnant women with a history of major depression who were either on antidepressants or had received antidepressants less than 12 weeks prior to their last menstrual period and were in remission.

• Women who discontinued antidepressant medication during pregnancy showed a significant increase in relapse of their major depression compared to those women who remained on antidepressant medication throughout pregnancy.
Time to Depression Relapse for Medication Maintenance vs. Discontinuation

5-fold increased risk of relapse for discontinuation vs. maintenance

Time to Depression Relapse for Medication Reintroduction vs. No Reintroduction

Risks of Untreated Depression During Pregnancy

- Miscarriage
- Inadequate maternal weight gain
- Poor self-care
- Substance use
- Preeclampsia
- Postpartum depression
- Cesarean delivery

- Impaired fetoplacental function
- Preterm birth
- Low birth weight
- Small for gestational age
- Fetal distress
- Neonatal care unit admittance

Risk–Benefit Analysis: Depression vs. Antidepressants

No randomized controlled trials comparing risk of depression vs. antidepressants

- Inadequate maternal weight gain
- Poor maternal self-care
- Substance use
- Preeclampsia
- Impaired fetoplacental function
- Fetal distress
- Cesarean delivery
- Neonatal care unit admittance
- Postpartum depression

- Miscarriage
- Preterm birth
- Low birth weight
- Small for gestational age
- Long-term neurodevelopmental abnormalities?
- Cardiac defect
- Major malformation
- Persistent pulmonary hypertension?
- Postnatal adaptation syndrome

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# Treated vs. Untreated Depression: Propensity Score Matching

<table>
<thead>
<tr>
<th>Outcome Differences</th>
<th>SE-D – DE Difference</th>
<th>P-value</th>
<th>DE – Nonexposed Difference</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-section</td>
<td>0.03</td>
<td>0.01</td>
<td>0.01</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Birth weight, g</td>
<td>-32</td>
<td>0.05</td>
<td>-24</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gestational age, wk</td>
<td>38.8 (SE-D) vs. 39.1 (DE) vs. 39.2 (Nonexposed)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preterm birth</td>
<td>0.02</td>
<td>&lt;0.001</td>
<td>0.006</td>
<td>0.007</td>
</tr>
<tr>
<td>Birth weight &lt;10th percentile</td>
<td>0.005</td>
<td>0.51</td>
<td>0.007</td>
<td>0.005</td>
</tr>
<tr>
<td>Length of hospital stay, d</td>
<td>0.43</td>
<td>0.007</td>
<td>0.12</td>
<td>0.006</td>
</tr>
<tr>
<td>Hospital stay &gt;3 d</td>
<td>0.05</td>
<td>&lt;0.001</td>
<td>0.01</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Respiratory distress</td>
<td>0.063</td>
<td>&lt;0.001</td>
<td>0.004</td>
<td>0.07</td>
</tr>
<tr>
<td>Feeding problems</td>
<td>0.015</td>
<td>0.002</td>
<td>0.003</td>
<td>0.02</td>
</tr>
<tr>
<td>Jaundice</td>
<td>0.019</td>
<td>0.01</td>
<td>-0.004</td>
<td>0.08</td>
</tr>
<tr>
<td>Convulsions</td>
<td>0.0005</td>
<td>0.64</td>
<td>-0.0002</td>
<td>0.49</td>
</tr>
</tbody>
</table>

1Incidence. 2For gestational age. 3Also significant for subgroup born vaginally.

SE-D: depressed, treated w/ SSRI. DE: depressed, not treated w/ medication.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Unmatched Difference</th>
<th>P-value</th>
<th>Propensity score matched Difference</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-section</td>
<td>0.03</td>
<td>0.01</td>
<td>-0.009</td>
<td>0.69</td>
</tr>
<tr>
<td>Birth weight, g</td>
<td>-32</td>
<td>0.05</td>
<td>10</td>
<td>0.72</td>
</tr>
<tr>
<td>Gestational age, wk</td>
<td>-0.35</td>
<td>&lt;0.001</td>
<td>-0.14</td>
<td>0.18</td>
</tr>
<tr>
<td>Preterm birth</td>
<td>0.02</td>
<td>&lt;0.001</td>
<td>0.007</td>
<td>0.61</td>
</tr>
<tr>
<td>Birth weight &lt;10\text{th} percentile</td>
<td>0.005</td>
<td>0.51</td>
<td>0.033</td>
<td>0.02</td>
</tr>
<tr>
<td>Length of hospital stay, d</td>
<td>0.43</td>
<td>0.007</td>
<td>0.055</td>
<td>0.83</td>
</tr>
<tr>
<td>Hospital stay &gt;3 d</td>
<td>0.05</td>
<td>&lt;0.001</td>
<td>0.037</td>
<td>0.07</td>
</tr>
<tr>
<td>Respiratory distress\textsuperscript{1,3}</td>
<td>0.063</td>
<td>&lt;0.001</td>
<td>0.044</td>
<td>0.006</td>
</tr>
<tr>
<td>Feeding problems\textsuperscript{1}</td>
<td>0.015</td>
<td>0.002</td>
<td>0.011</td>
<td>0.28</td>
</tr>
<tr>
<td>Jaundice\textsuperscript{1}</td>
<td>0.019</td>
<td>0.01</td>
<td>0.01</td>
<td>0.45</td>
</tr>
<tr>
<td>Convulsions\textsuperscript{1}</td>
<td>0.0005</td>
<td>0.64</td>
<td>0.00077</td>
<td>0.30</td>
</tr>
</tbody>
</table>

\textsuperscript{1}Incidence. \textsuperscript{2}For gestational age. \textsuperscript{3}Also significant for subgroup born vaginally.

SE-D: depressed, treated w/ SSRI. DE: depressed, not treated w/ medication.

Treated vs. Untreated Depression: Prospective Data

- Study 1: increased risk of lower gestational age and preterm birth with prenatal antidepressant use but not with untreated depression
  - Natural design; N=90; treated vs. untreated vs. control; comparable levels of depression in both treated and untreated groups

- Study 2: increased risk of preterm birth for both prenatal antidepressant use and untreated depression
  - Natural design; N=238; treated vs. untreated vs. control; lower depression levels in treated group

Why Is it So Hard to Interpret Study Results?

• Different methodologies, each with limitations
  – Retrospective case-control: recall bias, high nonresponse rate
  – Prospective interview: small sample size
  – Drug registry: unclear if patients actually took the drug as prescribed

• Untreated disorder as a confounding factor
  – Carries risks as well
  – Severity may be related to medication use
  – Drugs may be used for different disorders

Antidepressants During Pregnancy: Summary

• Possible small absolute risk of major malformations

• Possible small absolute risk of PPHN

• 20–30% rate of PNAS in exposed infants

• Unclear long-term neurodevelopmental effects

• Possible increased risk of lower gestational age (clinical significance?) and preterm birth
Preconception Planning for Patients on an Antidepressant: Guidelines

1. Moderate to severe symptoms?
   - No
   - Yes: Consider period of stability before attempting to conceive

2. Started antidepressant <6 months ago?
   - No
   - Yes: Consider period of stability before attempting to conceive

3. Recurrent episodes of MDD?
   - No
   - Yes: Previously responded to psychotherapy?
     - Yes: Consider continuation unless patient wants to discontinue
     - No: Patient may be eligible for a trial off medication with referral for psychotherapy, unless she wants to continue

Untreated Pregnant Patients With a Current MDE: Guidelines

Patient willing to consider pharmacotherapy?

- No
- Yes

Patient may be eligible for psychotherapy alone

Treated with psychotherapy in the past?

- No
- Yes

Failed to respond to psychotherapy?

- No
- Yes

Consider treatment with an antidepressant, assuming patient assessment and history do not reveal evidence of bipolar disorder

Pregnant Patients on an Antidepressant: Guidelines

Patient considering discontinuing pharmacotherapy?
- No
  - Continue antidepressant; monitor
- Yes
  - Treated with psychotherapy in the past?
    - No
      - No
        - Does the patient have current moderate to severe symptoms?
          - No
            - Previously relapsed after stopping antidepressant?
              - No
                - Consider taper; monitor
              - Yes
                - Consider psychotherapy; reevaluate medication need
          - Yes
            - Failed to respond or relapsed with psychotherapy in the past?
              - No
                - No
                  - Continue antidepressant; monitor
              - Yes
                - Yes
                  - Yes
                    - Consider taper; monitor
### FDA Use-in-Pregnancy Categories for Antidepressants (for What They're Worth)

<table>
<thead>
<tr>
<th></th>
<th>B</th>
<th>C</th>
<th>D</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>maprotiline</td>
<td>amitriptyline</td>
<td>milnacipran</td>
</tr>
<tr>
<td></td>
<td></td>
<td>amoxapine</td>
<td>mirtazapine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>bupropion</td>
<td>nefazodone</td>
</tr>
<tr>
<td></td>
<td></td>
<td>citalopram</td>
<td>phenelzine</td>
</tr>
</tbody>
</table>

**Preferred / Most Data:**

- fluoxetine (not during lactation)
- sertraline
- paroxetine
- citalopram

Depression Treatment Guidelines

- SSRIs are generally considered first-line in pregnancy
- Strongly consider an antidepressant that the woman is currently responding to or has responded to in the past to avoid unnecessary exposures during pregnancy
- Use lowest possible dose, but avoid undertreatment (could lead to dual exposure of drug and depression)
- Maximize non-medication evidence-based treatments
- Avoid polypharmacy unless it is clearly indicated
- Tapering antidepressants in the third trimester has not been shown to decrease the incidence of postnatal adaptation syndrome or improve infant outcomes*

Shared Decision Making

• Provide the patient with the information needed to make an informed decision
• Involve the family (father, grandparents)
• Ensure proper communication with other care providers
• Confirm that the patient has a support system
If a Patient Chooses to Discontinue Her Antidepressant: General Management

• Advise to resume antidepressant treatment shortly after delivery in order to mitigate the risk of postpartum depression

• Advise to report the onset of any depression-related symptoms

• Schedule follow-up appointment

• Communicate with the OBGYN
If a Patient Chooses to Discontinue Her Antidepressant: "Stimulating" Treatments

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Evidence in Pregnancy or Postpartum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychotherapy</td>
<td>1 positive randomized trial with IPT in postpartum depression(^1)</td>
</tr>
<tr>
<td></td>
<td>1 positive open-label trial of partner-assisted IPT in perinatal and postpartum depression(^2)</td>
</tr>
<tr>
<td>Exercise</td>
<td>1 positive randomized study (N=80) in pregnant women with no history of depression(^3)</td>
</tr>
<tr>
<td>Bright light therapy</td>
<td>1 positive small open-label trial in perinatal depression(^4)</td>
</tr>
<tr>
<td></td>
<td>1 positive small randomized trial in perinatal depression(^5)</td>
</tr>
<tr>
<td></td>
<td>1 negative small randomized trial in perinatal depression(^6)</td>
</tr>
</tbody>
</table>

If a Patient Chooses to Discontinue Her Antidepressant: "Stimulating" Treatments

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Evidence in Pregnancy or Postpartum</th>
</tr>
</thead>
<tbody>
<tr>
<td>rTMS</td>
<td>Positive published case reports(^1)</td>
</tr>
<tr>
<td></td>
<td>1 positive small open-label trial(^2)</td>
</tr>
<tr>
<td>ECT</td>
<td>Positive published case reports(^3) - (^5)</td>
</tr>
<tr>
<td>Acupuncture</td>
<td>1 positive randomized trial (N=150) in perinatal depression(^7)</td>
</tr>
<tr>
<td></td>
<td>1 small negative trial in postpartum depression(^8)</td>
</tr>
</tbody>
</table>

If a Patient Chooses to Discontinue Her Antidepressant: Herbal Treatments

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Evidence in Pregnancy or Postpartum</th>
</tr>
</thead>
</table>
| Omega-3            | 1 positive small double-blind trial in perinatal depression\(^1\)  
|                    | 3 negative double-blind trials (N=118) in perinatal depression\(^2\)-\(^4\)                           |
| Folate             | Prospective chart review (N=6809) was negative for perinatal depression but positive for postpartum depression at 21 months\(^5\) |
| Thyroid hormone    | Not studied; subset of patients may have abnormal thyroid levels                                     |
| Vitamin D          | Not studied; low vitamin D levels have been associated with perinatal depression\(^6\)            |

ANTIDEPRESSANT USE POSTPARTUM
Risk Factors for Postpartum Depression

- Previous major depressive episode
- Untreated depression during pregnancy
- Life stress
- Lack of social support
- Family history of postpartum depression

Risks of Postpartum Depression

- Disruption of maternal–infant bonding
- Self-harm
- Harm to infant

- Difficult temperament
- Attachment insecurity
- Cognitive delay
- Developmental delay
- Behavioral problems
- Difficulty with social interaction

Drug Exposure in Breast Milk

- Exposure can vary between women and within the same woman at different times
  - Drug characteristics (lipid solubility, dose, metabolism)
  - Genetic influence (enzyme activity of mother/child)
  - Timing of feeding vs. medication ingestion

## Antidepressants and Lactation

<table>
<thead>
<tr>
<th>Drug (~Descending Order of Available Data)</th>
<th>Relative Infant Dose (%)*</th>
<th>Relative Infant Plasma Concentration (%)**</th>
</tr>
</thead>
<tbody>
<tr>
<td>fluoxetine</td>
<td>6.5–11</td>
<td>up to 80</td>
</tr>
<tr>
<td>sertraline</td>
<td>0.5–3</td>
<td>--</td>
</tr>
<tr>
<td>paroxetine</td>
<td>0.5–3</td>
<td>--</td>
</tr>
<tr>
<td>citalopram</td>
<td>3–10</td>
<td>up to 10</td>
</tr>
<tr>
<td>fluvoxamine</td>
<td>&lt;2</td>
<td>--</td>
</tr>
<tr>
<td>venlafaxine</td>
<td>6–9</td>
<td>up to 30</td>
</tr>
<tr>
<td>escitalopram</td>
<td>3–6</td>
<td>&lt;4</td>
</tr>
<tr>
<td>mirtazapine</td>
<td>0.5–3</td>
<td>&lt;1</td>
</tr>
<tr>
<td>bupropion</td>
<td>2</td>
<td>--</td>
</tr>
<tr>
<td>duloxetine</td>
<td>&lt;1</td>
<td>--</td>
</tr>
<tr>
<td>desvenlafaxine</td>
<td>5.5–8.1</td>
<td>--</td>
</tr>
</tbody>
</table>

*Infant dose (mg/kg/d) divided by maternal dose (mg/kg/d). Value <10% is considered negligible.

**Infant plasma concentration divided by maternal plasma concentration OR by what is considered a low therapeutic adult concentration.

# Antidepressant Use During Pregnancy and Lactation

<table>
<thead>
<tr>
<th>L1 (safest)</th>
<th>L2 (safer)</th>
<th>L3 (moderately safe)</th>
<th>L4 (possibly hazardous)</th>
<th>L5 (contra-indicated)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>amitriptyline amoxapine clomipramine desipramine desvenlafaxine duloxetine escitalopram fluoxetine fluvoxamine imipramine maprotiline mirtazapine milnacipran nefazodone nortriptyline paroxetine protriptyline selegiline sertraline venlafaxine tranylcypromine trimipramine</td>
<td>bupropion citalopram doxepin escitalopram fluoxetine* mirtazapine nefazodone maprotiline venlafaxine</td>
<td>doxepin</td>
<td></td>
</tr>
</tbody>
</table>

*Neonates only; L2 in older infants. Categories were not identified for desvenlafaxine, duloxetine, isocarboxazid, milnacipran, phenelzine, protriptyline, selegiline, tranylcypromine, or trimipramine.

Breastfeeding Treatment Guidelines

Generally preferred
• Sertraline and paroxetine
  – Most data
  – Negligible relative infant doses/concentrations

Generally not preferred
• Fluoxetine, venlafaxine, and citalopram
  – Highest infant plasma concentrations (flu, ven)
  – Case reports of possible adverse effects (flu, cit)

After 3–6 months of age, the capacity to metabolize drugs is matured, and measurable infant plasma levels are not expected (Metabolic capacity takes longer to mature in preterm infants)

Breastfeeding Treatment Guidelines (cont.)

• Generally not necessary to recommend that women needing antidepressants abstain from breastfeeding

• Although some agents are less preferred, they can be considered in women who took them during pregnancy or have had previous effectiveness with them

• Often recommended to take the medication immediately after breastfeeding and prior to the infant's sleep time in order to minimize exposure to peak drug concentrations
  – Likely only reduces infant drug intake to a small extent

• No benefit of "pump and dump"

• Infants should be monitored for adverse effects, such as sedation, irritability, or change in sleep/feeding pattern

If a Patient Does Not Want to Take Medication While Breastfeeding

• "Breast is best"; however, the risks of untreated postpartum depression may well outweigh the benefits of breastfeeding

• Can consider nonpharmacological treatment

• If nonpharmacological treatment is unavailable or considered insufficient, encourage bottle feeding over treatment discontinuation

• Support the mother in her decision and monitor her carefully
Summary

• Existing data suggest that the benefits of antidepressant treatment during pregnancy and postpartum may outweigh the risks

• Breastfeeding does not need to be discontinued if antidepressants are used postpartum

• Whether or not to treat with antidepressants should be a shared decision between a clinician and an informed patient

• Ultimately, the decision belongs to the patient; support her as an ally and offer alternative treatment suggestions if needed
A Quick Word on Antipsychotics

• Haloperidol is most frequently used

• Best-studied atypical antipsychotics are olanzapine, risperidone, quetiapine, and clozapine

• Exposure to antipsychotics during the last gestational week may cause postnatal disorders