Antidepressant Drugs in Breastfeeding Mothers

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Depression in Pregnancy

* Between 14% and 23% of pregnant women experience a depressive disorder while pregnant.
* High rebound rate for moms who discontinue SSRIs (67%)
* In 2013 approximately 13% took antidepressants
* Risks higher is those who use Alcohol, Nicotine, or have poor prenatal care.
* PTSD = 8% of pregnant women
* No studies are available that link maternal depression to congenital anomalies in their infants.
* Dosing in Pregnancy: SAME as for non-pregnant

Antidepressants and Birth Outcomes

* Depressed moms generally take lots of drugs
* SSRIs are common; TCAs and MAOis infrequent
* Miscarriage: 8.7% no drugs, 12.4% with depression
* “Some” studies show reduced birth weight although not necessarily SGA (probably preterm).


Poor Neonatal Adaptation (Discontinuation Syndrome)

* Symptoms include: respiratory distress, cyanosis, apnea, seizures, temperature instability, etc.
* While tapering med in 3rd trimester may reduce these symptoms, must be done cautiously, however.
* PNA is common in shorter half-life SSRIs
* 15-30% with Paroxetine and Sertraline
* Symptoms include: tachypnea, hypoglycemia, temperature instability, irritability, weak cry, seizures rarely
* Pulmonary hypertension (right to left shunt)
  * 0.5 to 6 per thousand
  * Symptoms in infants are transient: resolved by 2 weeks
### Postpartum Depression

- Life Time Incidence of Depression is about 8.3-17%.
- Incidence Postpartum is 15%.
- Prior history of depression, risk 25-50% postpartum.
- Other risk factors:
  - Poor social support, Major stress factors during pregnancy
  - Family history of depression, Gestational diabetes
  - Gestational depression
- 2-3 times more prevalent in females.
- Highest incidence at 25-44 years.
- Slightly familial - 8-18% have one first degree relative with depression.

### Timing of the Baby Blues, Postpartum Depression (PPD), and Postpartum Psychosis

<table>
<thead>
<tr>
<th></th>
<th>Baby Blues</th>
<th>PPD</th>
<th>Postpartum Psychosis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prevalence</strong></td>
<td>40-80%</td>
<td>10-15%</td>
<td>0.2%</td>
</tr>
<tr>
<td><strong>Onset</strong></td>
<td>2-3 days</td>
<td>Onset within first month postpartum</td>
<td>Onset within 2-4 wk postpartum</td>
</tr>
<tr>
<td><strong>Duration</strong></td>
<td>Lasts less than 10 days</td>
<td>&gt;2 wks to months</td>
<td>&gt;4 d to months</td>
</tr>
<tr>
<td><strong>Suicide ideation</strong></td>
<td>Not present</td>
<td>May be present</td>
<td>Present</td>
</tr>
</tbody>
</table>

### Differential Diagnosis

<table>
<thead>
<tr>
<th>Baby Blues</th>
<th>PPD</th>
<th>Psychosis (postpartum)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feeling overwhelmed</td>
<td>Poor sleep</td>
<td>Delusional (e.g., baby is defective or dying, infant is Satan or God)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>Depressed mood</td>
<td>Auditory hallucinations that instruct her to harm herself or her infant.</td>
</tr>
<tr>
<td>Mood lability</td>
<td>Weight change (loss, gain)</td>
<td>Agitation</td>
</tr>
<tr>
<td>Depression</td>
<td>Feeling of guilt or worthlessness</td>
<td>Unusual thoughts or behaviors Hallucinations</td>
</tr>
<tr>
<td>Irritability</td>
<td>Anxiety</td>
<td>Hyper-sexuality</td>
</tr>
<tr>
<td>Difficulty sleeping</td>
<td>Difficulty sleeping but tired</td>
<td>Confusion/disorientation</td>
</tr>
<tr>
<td>but tired</td>
<td>Suicidal/infantidal thoughts</td>
<td></td>
</tr>
</tbody>
</table>

### Postpartum Depression in New Mothers

- Depressed mothers are more likely to:
  - Have negative attitudes about their infants.
  - Suggest they are more difficult and demanding infants.
  - Engage with their infant poor.
  - These early interruptions may affect maternal-infant bonding and development.
- Children may exhibit:
  - Sleep and eating problems
  - Hyperactivity
  - Cognitive delay
  - Emotional instability
- Past hesitancy in using antidepressants is lessening due to studies that show that postpartum depression interferes with optimal parenting and neurobehavioral development of children at one year.
**Unique Traits of Antidepressants**

- Not addictive in the usual sense
- Tolerance does not normally occur.
- No “Buzz” associated with their use.
- Occasional mild withdrawal occurs with shorter acting agents.
- They are ‘Slow’ in onset, usually 3 weeks, maybe 3 months prior to full benefit.
- Most side effects “wane” after 4-8 weeks.
- About 60-70% of patients respond positively.

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**Weight Gain with Antidepressants**

**Higher gain**

![Graph showing weight gain with antidepressants](image)

- Citalopram
- Escitalopram
- Fluoxetine
- Sertraline
- Paroxetine
- Bupropion
- Amitriptyline or Nortriptyline

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**Tricyclic Antidepressants**

- Less popular due to:
  - more anticholinergic side effects (dry mouth, constipation)
  - Extraordinarily dangerous in overdose
- Effective for:
  - patients who have used previously
  - younger patients
  - less expensive
  - equally efficacious to SSRIs
  - used for chronic pain syndromes, migraine prophylaxis, etc.

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**Choosing an Antidepressant**

( use the one that works!!!)

- **First Line Agents**
  - SSRIs
  - Zoloft, Paxil, Luvox, Lexapro, ………Prozac
  - Selective Serotonin + Norepinephrine RIs
  - Effexor
  - Cymbalta
  - Atypical Antidepressants
  - Bupropion (Wellbutrin, Zyban)
- **Second Line**
  - Tricyclics
  - Desipramine, Nortriptyline
- **Last Line……MAO inhibitors**
Onset of Antidepressant Effects with SSRIs

- **First Week**
  - Improvements in sleep and anxiety often evident in first week.
- **Second and Third Week**
  - Improvement in motivation, interests, hopefulness, and appetite
- **Fourth to Sixth Week**
  - Antidepressant, Antianxiety effect
  - Side effects wane
  - Impaired sexual function: decreased desire or libido, impaired arousal, erectile dysfunction, and delayed or absent orgasm.

Serotonin Reuptake Inhibitors (SSRIs)

- Prozac (fluoxetine)
- Zoloft (sertraline)
- Paxil (paroxetine)
- Luvox (fluvoxamine)
- Effexor (venlafaxine)
- Celexa (citalopram)
- Lexapro (escitalopram)
- Edronax (reboxetine)
- Vilazodone (Viibryd)
- Vortioxetine (Trintellix)

Kinetics of SSRIs

<table>
<thead>
<tr>
<th>Medicine</th>
<th>T1/2 (Parent)</th>
<th>T1/2 (metabolite)</th>
<th>Metabolite Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prozac</td>
<td>&lt; 72 hrs</td>
<td>223 hrs</td>
<td>100%</td>
</tr>
<tr>
<td>Paxil</td>
<td>15 hrs</td>
<td></td>
<td>0 %</td>
</tr>
<tr>
<td>Zoloft</td>
<td>26 hrs</td>
<td>96</td>
<td>0 %</td>
</tr>
<tr>
<td>Effexor</td>
<td>5 hrs</td>
<td>11 hrs</td>
<td>100 %</td>
</tr>
<tr>
<td>Celexa</td>
<td>36 hrs</td>
<td></td>
<td>0 %</td>
</tr>
<tr>
<td>Edronax</td>
<td>13 hrs</td>
<td></td>
<td>0 %</td>
</tr>
<tr>
<td>Lexapro</td>
<td>36 hrs</td>
<td></td>
<td>0 %</td>
</tr>
<tr>
<td>Brintellix (vortioxetine)</td>
<td>66 hrs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluoxetine (Prozac)</td>
<td>12 hrs</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The serotonin:norepinephrine ratios of SSRIs are as follows: venlafaxine = 30:1, duloxetine = 10:1, desvenlafaxine = 10:1, milnacipran = 1:3, and levomilnacipran = 1:2.

Fluoxetine (Prozac)

- Has long half-life “active” metabolite (223 hrs)
- >12+ studies with > 190 infants in the literature
  - concentration in milk levels varies from 28.8 to 181 ug/Liter of milk for fluoxetine, and 41.6 to 199 ug/Liter for norfluoxetine
- RID range = 1.5 – 14.6 %
- Infant plasma levels drop over first month
- Discontinuation syndrome probably slower in onset
- Overall, probably safe to use
- Minimal risk of discontinuation syndrome.
<table>
<thead>
<tr>
<th><strong>Sertraline (Zoloft)</strong></th>
<th><strong>Paroxetine (Paxil)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Many full term infants studied with sertraline.</td>
<td>More than 64 mother/infant pairs studied</td>
</tr>
<tr>
<td>No or limited data on Preterm Infants</td>
<td>Really quite safe in breastfeeding mothers.</td>
</tr>
<tr>
<td>Milk concentrations</td>
<td>If it works for mom, good choice in breastfeeding.</td>
</tr>
<tr>
<td>Relative infant dose = 0.4 to 2.2%</td>
<td>Highest rate with postpartum withdrawal in infant</td>
</tr>
<tr>
<td>Even Platelet function is not altered in infants.</td>
<td>RID range = 1.25 to 2.8%</td>
</tr>
<tr>
<td>In most infants, plasma levels of sertraline were below limit of detection (&lt; 2 ng/mL)</td>
<td>The drug was not detected in the plasma of most infants.</td>
</tr>
<tr>
<td>Preferred at this time, some weight loss may occur.</td>
<td>Neonatal withdrawal syndrome is worst with this drug.</td>
</tr>
<tr>
<td>Postnatal withdrawal reactions have been reported.</td>
<td>Do not use in adolescents due to risk of suicide</td>
</tr>
<tr>
<td>Withdrawal rate about 30%</td>
<td></td>
</tr>
<tr>
<td>No problems with withdrawal.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Citalopram (Celexa)</strong></th>
<th><strong>Escitalopram (Lexapro)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>M:P ratio is 3</td>
<td>Active metabolite of Celexa (citalopram)</td>
</tr>
<tr>
<td>RID Dose = 0.4% to 5.37% of maternal dose</td>
<td>Following 10 mg/day dose</td>
</tr>
<tr>
<td>At three weeks</td>
<td>M/P ratio = 2.2</td>
</tr>
<tr>
<td>Maternal serum = 185 nM ... Infant serum = 7 nM</td>
<td>RID = 5.18 – 7.9%</td>
</tr>
<tr>
<td>Mean M/P ratio is 1.6 – 3.0.</td>
<td>Infant plasma levels were below limit of detection (&lt; 3 µg/Liter)</td>
</tr>
<tr>
<td>Citalopram was detected in plasma from three infants (2, 2.3 and 2.3 µg/L).</td>
<td>Appears safe. Preferred over Citalopram (Celexa)</td>
</tr>
<tr>
<td>Manufacturer reports two cases of somnolence in breastfed babies.</td>
<td></td>
</tr>
<tr>
<td>Probably OK to use, just watch somnolence.</td>
<td></td>
</tr>
</tbody>
</table>

Mixed function serotonin and norepinephrine reuptake inhibitor
Useful for:
- Severe melancholia and depression, OCD, panic disorders, eating disorders, ADD, pain disorders.
- RID = 6.4 to 8.1% of maternal dose
- Infants were unaffected.
- New similar product = Cymbalta

Venlafaxine (Effexor)

SNRI
- Major Depressive Disorder (MDD)
- Generalized Anxiety Disorder (GAD)
- Diabetic Peripheral Neuropathic Pain (DPNP)
- Chronic Musculoskeletal Pain
- RID lower than other SNRI
- RID = 0.1% - 1.1%

Duloxetine

SSRIs in Breastmilk

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Relative Infant Dose [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amitriptyline (Elavil)</td>
<td>1.9% - 2.8</td>
</tr>
<tr>
<td>Bupropion (Wellbutrin)</td>
<td>0.2% - 2</td>
</tr>
<tr>
<td>Citalopram (Celexa)</td>
<td>3.56% - 5.17</td>
</tr>
<tr>
<td>Desipramine (Norpramin)</td>
<td>0.3% - 0.9</td>
</tr>
<tr>
<td>Duloxetine (Effexor)</td>
<td>3.2% - 3</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>5.2% - 7.9</td>
</tr>
<tr>
<td>Fluoxetine (Prozac)</td>
<td>1.0% - 14.6</td>
</tr>
<tr>
<td>Paroxetine (Paxil)</td>
<td>1.2% - 2.8</td>
</tr>
<tr>
<td>Sertraline (Zoloft)</td>
<td>0.4% - 2.2</td>
</tr>
<tr>
<td>St. John’s wort</td>
<td>No data</td>
</tr>
<tr>
<td>Venlafaxine (Effexor)</td>
<td>0.8% - 8.1</td>
</tr>
</tbody>
</table>

Other New Antidepressants

- Vortioxetine (Brintellix) (No Data yet)
- Indication major depressive order.
- Especially good in geriatric patients
- Levomilnacipran (Fetzima)
- NRSI (more norepinephrine than 5HT)
- Neuropathy, depression, fibromyalgia
- Vilazodone (Vibryd)
- No data yet.
**Bupropion (Zyban, Wellbutrin)**

- Bupropion action is largely unknown. Probably dopamine and serotonin agonist.
  - Bupropion Serum Levels
    - Mother1 & 2 = 55 and 44 ng/mL
    - Infant1 = < 5 ng/mL (undetectable)
    - Infant2 = < 10
  - RID range = 0.2 – 2.0%
  - Observe closely for reduced milk supply.
  - NEVER use in patients with seizure disorders, even in the past.

**St.-John’s Wort**

- Hypericin was undetectable
- Hyperforin levels varied from undetectable to 18.2 ng/mL
- Virtually devoid of side effects but is a mild photosensitizing agent.
- Meta analyses show antidepressant effects in 70% of patients.
  - Side effects in only 20% of patients compared to 53% on conventional antidepressants (TCA).
- Also contains sedative properties, suppresses anxiety.
- Numerous Drug-Drug interactions
  - Stimulates Cytochrome P450 to metabolize:
    - HIV protease inhibitors, Cyclosporine, Anticonvulsants, Birth control pills ???
- Considered a WEAK antidepressant.

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**Risk Assessment of Antidepressants**

- Recent studies show NO risk of ADHD

- Data is significant and clearly suggests infant outcome is OK.
- Use the antidepressant that works best!!!
- Infants Exposed in utero probably will do better if continue to breastfeed !!
Bipolar Disorders

Mania + Depression

* Bipolar disorder is a diagnosis describing low (clinically depressed) and high (manic or hypomanic) mood swings

* Symptoms of Mania include:
  * Inflated self-esteem or grandiosity
  * Elevated, expansive, irritable mood
  * Decreased need for sleep
  * More talkativeness
  * Reckless, foolish activities

**Drugs for Mania**
- Lithium
- Olanzapine (Zyprexa)
- Aripiprazole (Abilify)
- Valproic acid (works well but poor choice)
- Lamotrigine (Lamictal)
- Carbamazepine (Tegretol)
- Rarely: SSRIs

**Therapy With Lithium**
- GOLD Standard, works well and effectively.
- Patients hate it.
- Lithium transfers readily into human milk.
- Slow...Takes 2-3 weeks for activation.
- Infant levels approach 30-40% of maternal levels
- Relative Infant dose = 12 – 7.8%
- May be higher in premature infants, suggest waiting until renal clearance is better.
- Clinicians must keep mom in normal range
  - < 1.1 mEq
  - Occasional monitoring of infant recommended
  - Monitor infant thyroid function.
- New therapies include: Lamotrigine

**Bipolar Therapy in Breastfeeding Mothers**
- Lithium can be hazardous.
- HCP must follow infant closely and monitor levels routinely.
- Preferred Agents
  - Lamotrigine (Lamictal)
  - Supplement moms with folic acid who take valproic acid, carbamazepine, oxcarbazepine
- Atypical Antipsychotics
  - Quetiapine, Risperidone, Aripiprazole
- Potential risk of diabetes
**Bipolar Meds**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Relative Infant Dose (RID) %</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valproic Acid</td>
<td>0.9 - 5.6%</td>
<td>Hazardous: Do not use in young women at risk of pregnancy or breastfeeding. If absolutely required, supplement with Folic Acid. NERAD study demonstrated adverse cognitive effects from valproic acid exposure in utero. IQ deficits are 8-11 IQ points.</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>3.8 - 5.9</td>
<td>Compatible: Levels in milk are reported to be low (2.8-4.5mg/L), the estimated infant dose is less than 0.68 mg/kg/day. One report of cholestasis function tests occurred in a 9 day-old infant. Supplement with Folic acid.</td>
</tr>
<tr>
<td>Lithium</td>
<td>12 - 7.0%</td>
<td>Compatibility: Results in the infant. Infants plasma about 30-45% of maternal level.</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>9.2 - 18.2%</td>
<td>Compatible: Reports of significant plasma levels have occurred in some breastfed infants, although none have been high enough to produce side effects. It may be helpful to monitor the infant's plasma levels.</td>
</tr>
<tr>
<td>Topiramate</td>
<td>24.5 - 15.0%</td>
<td>Compatible: Levels in infants are 10-30% of maternal. No adverse effects have been reported in breastfed infants.</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>7.7</td>
<td>Compatible: Low amounts enter breast milk, monitor for sedation and infant levels can be done if symptoms occur.</td>
</tr>
</tbody>
</table>

**Treatment of Psychosis**

- Older Drugs studied thus far:
  - Chlorpromazine (Thorazine) (RID = 0.25%)
  - Chlorprothixene (Taractan) (RID = 0.15%)
- There is concern that phenothiazine family may increase risk of SIDS and sleep apnea.
- Promethazine (Phenergan)
- If you need an antiemetic use ondansetron (Zofran)
- Avoid this family, use atypical antipsychotics instead.

**Antipsychotics (Atypicals)**

- Risperidone (Risperdal)*
  - Less likely to induce extrapyramidal symptoms
  - RID = 2.8 to 9.1% of maternal dose.
- Olanzapine (Zyprexa)**
  - RID = 1.2% of the maternal dose.
- Quetiapine (Seroquel)
  - RID = < 0.1%
- Aripiprazole (Abilify)
  - RID = 1%
  - Observe for somnolence. Reduces PROLACTIN levels and may suppress milk production. (numerous calls about loss of milk).

**Problems with Atypical Antipsychotics**

- New found risk of Diabetes in adult patients
- Don’t know about breastfed infants
- Probably minimal?
- Neonatal apnea may be a problem, don’t know at this point.
- Massive weight gain in Adults and children
- Don’t know about breastfed infants?
- Aripiprazole will probably reduce prolactin

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### Atypical Antipsychotics

<table>
<thead>
<tr>
<th>Drug</th>
<th>Relative Infant Dose</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haloperidol</td>
<td>0.2% - 12%</td>
<td>Probably Compatible</td>
</tr>
<tr>
<td>Olanzapine (Zyprexa)</td>
<td>0.3% - 2.2%</td>
<td>Probably Compatible</td>
</tr>
<tr>
<td>Aripiprazole (Abilify)</td>
<td>1%</td>
<td>Caution loss of milk supply</td>
</tr>
<tr>
<td>Clozapine</td>
<td>1.33% - 1.4%</td>
<td>Probably Compatible</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>0.07% - 0.1%</td>
<td>Probably Compatible</td>
</tr>
<tr>
<td>Risperidone</td>
<td>2.8% - 9.1%</td>
<td>Probably</td>
</tr>
</tbody>
</table>

### Anxiety Disorders

- **Anxiety Disorders**
  - Generalized Anxiety Disorder
  - Panic Disorder
  - Social Phobia
  - Obsessive-Compulsive Disorder
  - Posttraumatic Stress Disorder

### Benzodiazepines Anxiolytics

- Initial Treatment ONLY. NMT several weeks.
- “Valium-like” drugs.
- Very effective but addictive.
- Brief anesthetic use OK.
- Day after day use may produce higher levels and perhaps somnolence and dependence.
- Suggest Clinicians use shorter half-life products
  - Lorazepam (Ativan)
  - Alprazolam (Xanax) caution, addictive.
- With addictive personalities, use BuSpar. Works slowly, but not addictive.

### Lorazepam (Ativan)

- Used in pregnant mothers, may see postnatal problems.
- Respiratory depression, hypothermia, feeding problems (Valium)
- RID = 2.6 - 2.9%
- Preferred benzodiazepine at present.
- Neonatal Withdrawal noted following prolonged exposure to breastmilk.
* RID = 8.4%

While milk levels are low, significant neonatal withdrawal reactions have been reported in breastfed infants and infants postpartum.

Addictive potential suggests this drug is less ideal for breastfeeding mothers.

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**Alprazolam (Xanax)**

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**Drugs of Choice**

SSRIs

- Sertraline (Zoloft) is probably best choice at this point.
- Paroxetine (Paxil) good choice if works for mom.
- Escitalopram (Lexapro) or Paroxetine (Paxil) are second choices.
- Venlafaxine (Effexor) is fourth choice.
- Prozac is probably OK, but lesser choice.

Antipsychotics

- Risperidone
- Quetiapine
- Olanzapine

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**Antidepressants**

- Women with breastfeeding infants are at high risk. Try your best to support them.
- Most antidepressants appear to be safe for breastfed infants.
- Long-term outcome appears normal, but studies are limited.
- To many of these women, breastfeeding is the best thing in their lives, help them keep this best part.

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**Breastfeeding and Antidepressants**

- Symptoms are minimal
- Moms apparently view infants more positively if consuming antidepressants.
- Problem: mom’s could be biased in that they want to rationalize their use of Antidepressants.
- Problem: the Antidepressants could be directly affecting the infant (unlikely).
- Or: the treated mother is a better mother and the baby responds to this…