Psychiatry Clinical Reviews
Perinatal Psychiatry: Beyond the Basics

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None

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None
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Off-Label/Investigational Uses
None
Learning Objectives

• Review epidemiology pertinent to bipolar disorder and pregnancy
• Review use of common classes of medications used during treatment of bipolar disorder during pregnancy and lactation:
  • Lithium
  • Anti-epileptic drugs
  • Antipsychotic medications
Risk of bipolar mood episode onset or relapse during pregnancy

- Peak incidence of bipolar disorders
  - For women, 12 – 30 years of age

- Period prevalence of bipolar disorders
  - Not significantly different between pregnant and non-pregnant women
  - Lower prevalence rates reported in NESARC (2001-2002) survey

- One-third of patients may have recurrence with continuation of effective pharmacotherapy (much higher if treatment is stopped)
High rates of puerperal recurrence in bipolar women, exceeding that of MDD

Data are from a prospective cohort study of 2,252 pregnancies in 1,162 women with BP-1, BP-2, or MDD

Obstetric and fetal risks associated with diagnosis of bipolar disorder

- Smoking, overweight, and substance use
- Toxicities (related to tobacco, alcohol, illicit drugs)
- Placental abnormalities
- Antepartum hemorrhages
- Low birth weight, SGA, small head circumference
- Neonatal dysglycemia
- Caeserian delivery
- Preterm delivery

Consequences of acute manic or depressive relapses

- Impulsive, risky behaviors
- Substance use
- Disrupted social supports
- Disrupted family functioning
- Psychiatric hospitalization
- Poor adherence to prenatal care
- Maternal suicide

Regier DA et al. JAMA 1990;264:2511
Curtis V. Bipolar Disord 2005;7 (suppl 1):16
Goldstein BI et al. Bipolar Disord 2008;10:469
Neurocognitive and psychiatric risks in offspring of women with bipolar disorder

- Affective, anxiety, and disruptive behavioral disorders
- Memory and attention disturbances
- Impaired social functioning

Henin A. Biol Psychiatry 2005;58:554
Duffy A et al. Bipolar Disord 2007;9:828
Hirschfeld-Becker DR et al. Psychiatry Res 2006;145:155
Pharmacotherapy in pregnancy: acute manic and mixed episodes

- **Good news**
  - Large number of reasonably effective treatments exist
  - No clear evidence that antimanic drugs are less effective in women than men

- **Bad news**
  - RCTs typically exclude pregnant women from participation

Data are from a systematic review of 68 randomized trials of pharmacotherapy for acute mania in adults (~16,000 patients)
Pharmacotherapy in pregnancy: acute depressive episodes

- **Good news**
  - Reasonably effective treatments for bipolar depression exist (though fewer than mania)
  - No clear evidence that drugs shown to be effective are less so for women

- **Bad news**
  - RCTs typically exclude pregnant women from participation
Pharmacotherapy in pregnancy: maintenance phase treatment and recurrence risk

- Recurrence rates substantially lower with continuation (30%-37%) vs. discontinuation (86%-100%) in prospective studies
- Relapses tend to occur early (first trimester); depressive or mixed polarity
- One naturalistic study reported lower overall relapse rates during pregnancy
- Rapid lithium discontinuation associated with higher relapse rates than gradual tapering (63% vs. 37%)

Pharmacotherapy in pregnancy: prevention of post-partum relapse

- Two retrospective studies suggest benefit
  - Viguera et al. (2000): lithium continuation associated with lower postpartum recurrence (33% vs. 70%)
  - Cohen et al. (1995): antimanic prophylaxis associated with lower rates of relapse or evidence of affective instability (7% vs. 62%)

- Marginal/no significant benefit reported in two small prospective studies
  - Bergink et al. (2012): during postpartum, 92% who continued medication and 80% who stopped remained well.
  - Wisner et al. (2004): lower level of hypomanic symptoms with VPA, but no significant difference in occurrence of depressed, manic, hypomanic, or mixed states between those who receive postpartum VPA and those who did not.
Risks of treatment with medication while pregnant

- Structural teratogenesis (CM’s)
- Adverse neonatal events
- Neuro-behavioral teratogenesis
How are risks of pharmacotherapy during pregnancy studied?

- No randomized trials; only observational studies
Confounding in studies of risk

Drug

RR > 1

RR ~ 1

Adverse birth outcomes

“Measured” confounding
(age, sex, race)
Restriction Stratification
Matching Adjustment
Weighting Combination

Unmeasured confounding
Other drugs, lifestyle factors, BMI*,
comorbid medical conditions, nutrition,
other pregnancy or health characteristics,
SES, smoking, maternal stress, genetic factors, obstetric factors, etc.
Confounding by indication

Drug

RR > 1

RR ~ 1

Adverse birth outcomes

"Measured" confounding
Bipolar disorder diagnosis

Unmeasured confounding
Bipolar disorder severity,
Time spent actively symptomatic,
Comorbid psychiatric disorders,
Bipolar disorder impact on prenatal care
and self-care, Presence/absence of psychosis, etc.
Lithium: structural teratogenesis

- Early retrospective studies
  - Suggested MCM rate of 11%; 400-fold increase in the risk of congenital heart disease, such as cases of Ebstein’s anomaly

- Later studies--more reassuring results
  - Prospective studies suggest MCM rate of 2.8%

- Meta-analysis
  - Absolute risk (Ebstein’s anomaly): 1 case per 1,000-2,000 births; 10-20 times the rate in general population

- Systematic review of published information about CM risk (1969-2005) – lithium is not considered a major human teratogen

References:
Schou M et al. Drug Saf 1998;18:143
Cohen LS et al. JAMA 1994;271:146
Yacoby S et al. Isr J Psy Related Sci 2008;45:95
Kallen B & Tandberg A. Acta Psych Sand 1983;68:134
Lithium: adverse neonatal events

- Later pregnancy exposure asssd. with a neonatal adaptation syndrome
  - **Clinical features:** Hypotonicity, cyanosis, lethargy, bradycardia/tachycardia, lower APGAR scores, seizures, poor feeding, poor suck/grasp/Moro
  - More severe with lithium level >0.6 mEq/L (in the neonate)
  - Resolves in 1-2 weeks, usually with full recovery; but can result in longer hospital stays
  - Long-term outcome uncertain

- Neonatal complications of LI use
  - **Obstetric:** Prematurity, LGA
  - **Neonatal:** hypothyroidism (reversible), non-toxic goiter, nephrogenic diabetes insipidus, polyhydramnios
Lithium: neurodevelopmental outcomes

- Not yet clearly associated with adverse neurodevelopmental or neurobehavioral outcomes
- Uncertain if LI neonatal adaptation syndrome is associated with an adverse long-term neurocognitive or neurodevelopmental course
Lithium

• May be safest choice, particularly with history of positive response and Bipolar I diagnosis

• Practical considerations:
  
  • For women with 1st trimester exposure: prenatal assessment for fetal anomalies, including fetal echocardiogram (16-18 wks of gestation)
  
  • Awareness of potential for acute perinatal toxicities with exposure later in gestation
  
  • Close monitoring of lithium levels during pregnancy & at delivery
  
  • Consider withholding lithium for 24-48 hours prior to delivery to improve neonatal outcomes; a scheduled delivery allows opportunity to temporarily suspend lithium therapy
Lithium: lactational safety

- Excretion in breast milk
  - Lithium is excreted at relatively high levels in breast milk
  - Infant serum levels up to 50% of maternal serum levels

- Reported adverse effects in nursing offspring
  - Cyanosis, hypotonia, hypothermia, lethargy, ECG changes

- Consensus and opinion
  - American Academy of Pediatrics: incompatible with breastfeeding
  - Theoretical risk: immature kidneys, dehydration → greater accumulation
  - Monitoring: signs of Li toxicity; Li levels, TSH, BUN, Cr (Q 6-8 weeks while child is nursing); avoid using blood tubes that contain lithium-heparin

Moretti ME et al. Ther Drug Monit 2003;25:364
Tunnessen WW, Hertz CG. J Pediatr 1972;81:804
Avoid lithium heparin blood collection tubes
Antiepileptic drugs (mood stabilizers) and congenital malformations

• Major congenital malformations (MCMs) are rare events → very large number of pregnancies needed
  - Need ~3,000 exposed infants to detect 3-fold increase in risk of defect occurring in 1/1,000 babies

• Very large patient registries:
  - Population-based: Sweden, Norway, Finland, Denmark
  - Specialty-based (epilepsy): North American AED Pregnancy Registry (NAAPR); UK Epilepsy and Pregnancy Register; EURAP (>40 countries)

  ▪ European Surveillance of Congenital Anomalies (EUROCAT)
  - Population based database, 14 European countries
Valproate: structural teratogenesis

- **Highest rates of overall MCM (WWE)**
  - Prevalence, any MCM: 5-11% in babies born to WWE who received VPA monotherapy (registry data)
  - Versus other AEDs: Higher rates of MCMs with VPA than carbamazepine or lamotrigine
  - Predominantly neural tube defects, 1-2% (10-fold increase over bkgd.)
  - Others: craniosynostosis, oral clefts, hypospadias, ASDs, polydactyly (EUROCAT)

- **Dose-dependency**
  - Significant associations between dose of VPA monotherapy and risk of fetal
  - Increased MCM risk above 800-1000 mg daily

- **Risks of combination therapy**
  - Increased MCM risk when VPA combined with other AEDs vs monotherapy

References:
- Harden CL et al. Epilepsia 2009;50:1237
- Wyszynski DF et al. Neurology 2005;64:961
- Diav-Citrin O et al. CNS Drugs 2008;22:325
Rates of major congenital malformations associated with AED monotherapy

Rates (95% CI) are presented. Data are from Tomson T et al. Lancet Neurol 2011;10:609.
Valproic Acid Monotherapy in Pregnancy and Major Congenital Malformations

Data Source
- 19 population-based European Surveillance of Congenital Anomalies (EUROCAT) registries in 14 countries
- 3,881,592 live births and stillbirths
- 98,075 major congenital malformations
- OR’s adjusted for maternal age, child’s birth year, individual registry

<table>
<thead>
<tr>
<th>Malformation type</th>
<th>Odds ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spina bifida</td>
<td>12.7</td>
<td>7.7 to 20.7</td>
</tr>
<tr>
<td>Craniosynostosis</td>
<td>6.8</td>
<td>1.8 to 18.8</td>
</tr>
<tr>
<td>Cleft palate</td>
<td>5.2</td>
<td>2.8 to 9.9</td>
</tr>
<tr>
<td>Hypospadias</td>
<td>4.8</td>
<td>2.9 to 8.1</td>
</tr>
<tr>
<td>Atrial septal defect</td>
<td>2.5</td>
<td>1.4 to 4.4</td>
</tr>
<tr>
<td>Polydactyly</td>
<td>2.2</td>
<td>1.0 to 4.5</td>
</tr>
</tbody>
</table>

Valproate: adverse neonatal events

- Neonatal toxicity syndrome
  - Irritability
  - Feeding problems
  - Heart rate decelerations
  - Abnormal muscle tone
  - Liver toxicity
  - Coagulopathies
  - Hypoglycemia

Valproate: neurodevelopmental outcomes

- Several studies show associate VPA exposure with adverse cognitive and developmental effects
  - Lower IQ scores with VPA vs. other AEDs in offspring (up to age 6)
  - Association between VPA and lower IQ is independent of maternal IQ

- Dose-dependency
  - Consistently shown with VPA, but not CBMZ or LTG
  - Increased risk above 800-1000 mg daily

- Risks of neurodevelopmental disorders
  - Poor adaptive functioning
  - ADHD, PDD spectrum disorders (up to age 6)
  - “Autistic traits” (up to age 4)
Valproate: lactational safety

- Excretion in breast milk
  - Valproate is excreted at relatively low levels in breast milk
  - Infant serum levels up to 6% of maternal serum levels

- Reported adverse effects in nursing offspring
  - One report of thrombocytopenia and anemia in nursing infant

- Consensus and opinion
  - American Academy of Pediatrics: compatible with breastfeeding
  - Theoretical risk: liver toxicity (<2 yo), neurodevelopmental toxicity
  - Monitoring: valproate levels, liver function tests (Q 2-4 weeks), neurodevelopmental screening tools (?)
### NEAD study

- Prospective cohort study (305 mothers, 311 children from UK and USA)
- Primary outcome: IQ at age 6 years (analyses adjusted for maternal IQ, dose, periconceptional folate, and gestational age)

#### Table 1

<table>
<thead>
<tr>
<th></th>
<th>Carbamazepine</th>
<th>Lamotrigine</th>
<th>Phenytoin</th>
<th>Valproate</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total-enrolled</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Participants</td>
<td>94 (30%)</td>
<td>100 (32%)</td>
<td>55 (18%)</td>
<td>62 (20%)</td>
</tr>
<tr>
<td>Mean IQ*</td>
<td>105 (102–108)</td>
<td>108 (105–110)</td>
<td>108 (104–112)</td>
<td>97 (94–101)</td>
</tr>
<tr>
<td>Difference</td>
<td>7 (3–12)</td>
<td>10 (6–15)</td>
<td>10 (5–16)</td>
<td>NA</td>
</tr>
<tr>
<td>p value†</td>
<td>0.0015</td>
<td>0.0003</td>
<td>0.0006</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Age-6-completers</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Participants</td>
<td>61 (27%)</td>
<td>74 (33%)</td>
<td>40 (18%)</td>
<td>49 (22%)</td>
</tr>
<tr>
<td>Mean IQ*</td>
<td>106 (103–109)</td>
<td>108 (105–111)</td>
<td>109 (105–113)</td>
<td>98 (95–102)</td>
</tr>
<tr>
<td>Difference</td>
<td>8 (3–13)</td>
<td>10 (6–15)</td>
<td>11 (5–16)</td>
<td>NA</td>
</tr>
<tr>
<td>p value†</td>
<td>0.0010</td>
<td>0.0003</td>
<td>0.0004</td>
<td>NA</td>
</tr>
</tbody>
</table>

Fetal antiepileptic drug exposure and cognitive outcomes at age 6 years (NEAD study): a prospective observational study

Effects of dose

- Higher- and lower-dose groups determined by median split
- Mean IQ significantly worse with higher-dose VPA vs. all other groups
- No significant difference between any CBMZ or LTG group vs. lower-dose VPA

<table>
<thead>
<tr>
<th>Drug</th>
<th>Below group median</th>
<th>Above group median</th>
<th>p value (vs below-median dose valproate)</th>
<th>p value (vs above-median dose valproate)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(median dose 700 mg per day)</td>
<td>28 107 (102–112)</td>
<td>33 106 (102–110)</td>
<td>0.3994</td>
<td>0.0002</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(median dose 433 mg per day)</td>
<td>31 106 (102–111)</td>
<td>43 109 (105–113)</td>
<td>0.4854</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Phenytoin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(median dose 398 mg per day)</td>
<td>20 108 (103–114)</td>
<td>20 106 (101–112)</td>
<td>0.2551</td>
<td>0.0002</td>
</tr>
<tr>
<td>Valproate</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(median dose 1000 mg per day)</td>
<td>23 104 (99–109)</td>
<td>26 94 (90–99)</td>
<td>NA</td>
<td>0.0065</td>
</tr>
</tbody>
</table>

Means were adjusted for maternal IQ, gestational age at birth, and folate. IQ = intelligence quotient.
**Carbamazepine: structural teratogenesis**

- Once considered highly teratogenic; more recent data suggests lower risk
  - **Prevalence, any MCM:** 2-6% in babies born to epileptic WWE who received carbamazepine monotherapy (registry data)
  - **Versus other AEDs:** Lower rates of MCMs with carbamazepine than valproate; higher than (but similar to) lamotrigine
  - Neural tube defects (spina bifida) – 2-3 per 1000 births (2.6-times higher than gen. popln.)
  - Other CMs: craniofacial defects, CV malformations, hypospadias, fingernail hypoplasia

- **Dose-dependency**
  - Recent EURAP study suggests possible association between carbamazepine dose and fetal malformation risk (Tomson, 2011)

- **Risks of combination therapy**
  - Higher rates of MCMs with carbamazepine when prescribed with VPA vs. carbamazepine alone

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Tomson T et al. Lancet Neurol 2011;10:609
Rates of specific malformations associated with AED monotherapy

Figures based on a review of 21 prospective studies (Tomson, 2012)
Carbamazepine: adverse neonatal events

- SGA and LBW
- Microcephaly
- Transient hepatotoxicity
- Vitamin K deficiency
- Coagulopathy
Carbamazepine: neurodevelopmental outcomes

- Overall risk is uncertain
  - Some studies show variable degrees of developmental delay
  - Most prospective studies do not suggest long-term cognitive problems or deficits

- Dose-dependency
  - NEAD study showed verbal performance at age 3 years was worse with increasing maternal carbamazepine dose during pregnancy (Meador, 2011)
Scatter plots of verbal and non-verbal index scores as a function of standardized AED dose during pregnancy

Carbamazepine: lactational safety

- Excretion in breast milk
  - Carbamazepine is excreted at relatively low levels in breast milk
  - Infant serum levels up to 15% of maternal serum levels (few cases)

- Reported adverse effects in nursing offspring
  - Case reports of hepatotoxicity in nursing infant

- Consensus and opinion
  - American Academy of Pediatrics: compatible with breastfeeding
  - No long-term neurodevelopmental data
  - Monitoring: carbamazepine levels, liver function tests (Q 2-4 weeks)

Lamotrigine: structural teratogenesis

• Not yet clear if lamotrigine increases risk of MCMs above baseline rate
  - **Prevalence, any MCM:** 2-3% in babies born to WWE who receive lamotrigine (registry data)
  - **Versus other AEDs:** Lower rates of MCMs with lamotrigine than VPA
  - Possible increase risk of oral clefts (9 per 1,000 births); but also negative reports

• **Dose-dependency**
  - Some report higher risk at doses >200 mg/day; also negative reports

References:
- Cunningham M, Tennis P. Neurology 2005;64:955
- Holmes LB et al. Neurology 2008;70:2152
- Morrow J et al. J Neurol Neurosurg Psych 2006;77:193
- Molgaard-Nielsen, Hviid A. JAMA 2011;305:1996
- Vajda FJ et al. Seizure 2010;19:558
- Dolk H et al. Neurology 2008;71:714
- Cunnington M et al. Neurology 2011;76:1817
Lamotrigine: adverse neonatal events

- Not yet clear if lamotrigine is associated with increased rates of adverse neonatal events
- Very few reports
Lamotrigine: neurodevelopmental outcomes

- Data are reassuring thus far (offspring of WWE up to age 6)
- No evidence of dose-dependent increase in risk of problems with adaptive and emotional/behavioral functioning
- No evidence of increased risk of neuro-developmental disorders (up to age 6)
- Very few reports, few independent cohorts
  - Practical take-away: Recommendation to maintain dose <200 mg/d during 1st and 2nd trimesters (but need to consider what dose has maintained euthymia)
  - But higher doses may be needed in 3rd trimester with increased renal clearance

Bromley RL et al. J Neurol Neurosurg Psych 2013;84:637
Lamotrigine: lactational safety

- **Excretion in breast milk**
  - Lamotrigine is excreted at relatively high levels in breast milk
  - Infant serum levels ~30% (range 23%-50%) of maternal serum levels

- **Reported adverse effects in nursing offspring**
  - No adverse effects reported in nursing infants

- **Consensus and opinion**
  - American Academy of Pediatrics: effects unknown but may be of concern
  - Theoretical risk: severe rash (including Stevens-Johnson Syndrome)
  - Monitoring: routinely for adverse effects

Ohman I et al. Epilepsia 2000;41:709
Liporace J et al. Epilepsy Behav 2004;5:102
Other antiepileptic drugs

- Examples
  - Gabapentin
  - Topiramate (*oral clefts?)
  - Levetiracetam
  - Pregabalin
  - Tiabagine
  - Zonisamide
  - Oxcarbazepine

- Reproductive safety data reassuring thus far, but very few reports*
- Unproved benefit for treating bipolar disorder (no further review)

Hernandez-Diaz S et al. Neurology 2012;78:1692
Rosa AR et al. CNS Neurosci Ther 2011;17:167
Cipriani A et al. Lancet 2011;378:1306
Typical antipsychotics: structural teratogenesis

- No clear association between typical antipsychotics and MCMs
  - 2 systematic reviews (Gentile, 2010; Einarson & Boskovic, 2009)
  - Most studied: haloperidol, chlorpromazine, perphenazine

Gentile S. Schizophr Bull 2010;36:518
Typical neuroleptics: lactational safety

- Excretion in breast milk
  - Excreted at varying levels in breast milk (chlorpromazine, perphenazine, trifluoperazine, haloperidol)

- Reported adverse effects in nursing offspring
  - Chlorpromazine: drowsiness, lethargy
  - Chlorpromazine + haloperidol: developmental delay

- Consensus and opinion
  - American Academy of Pediatrics: effects unknown but may be of concern
  - Lack of safety data have led some to recommend against breastfeeding while taking antipsychotic drugs: Theoretical risk: extrapyramidal effects. Monitoring: for sedation and other adverse effects
Antipsychotics and the risk of structural teratogenesis

13 cohort studies (10 independent cohorts)
Exposed (N=6,289 preg.); Unexposed (N=1,618,039 preg.)

## APDs and obstetric and neonatal outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>OR</th>
<th>95% CI</th>
<th>ARD</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spontaneous ab.</td>
<td>1.05</td>
<td>0.61 - 1.81</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stillbirth</td>
<td>1.18</td>
<td>0.88 - 1.57</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preterm delivery</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Typical</td>
<td>1.86</td>
<td>1.45 - 2.39</td>
<td>0.05</td>
<td>0.03 - 0.08</td>
</tr>
<tr>
<td>Atypical</td>
<td>2.03</td>
<td>1.47 - 2.80</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.61</td>
<td>1.15 - 2.25</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SGA</td>
<td>2.44</td>
<td>1.22 - 4.86</td>
<td>0.05</td>
<td>0.02 - 0.09</td>
</tr>
<tr>
<td>LGA</td>
<td>2.50</td>
<td>0.77 - 8.16</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### WMD 95% CI

| Gest. age (wks) | -0.31| -0.44 - 0.01 |
| Birth weight (g)| -57.89| -103.69, -12.10 |
Antipsychotic use and the risk of congenital malformations

Retrospective cohort study of 1,360,101 F Medicaid enrollees with a live-born infant (Medicaid Analytic Extract database, 2000-2010)

Exposures: first trimester, filled prescriptions
Endpoints: MCMs (ICD-9 codes, maternal and infant)

Table 3. Absolute Risk for Congenital Malformations in Women With and Without AP Exposure

<table>
<thead>
<tr>
<th>Exposure Group</th>
<th>Any Malformation</th>
<th>Cardiac Malformation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total No.</td>
<td>No. of Events</td>
</tr>
<tr>
<td>Unexposed</td>
<td>1,331,910</td>
<td>43,494</td>
</tr>
<tr>
<td>Typical AP</td>
<td>733</td>
<td>28</td>
</tr>
<tr>
<td>Atypical AP</td>
<td>9258</td>
<td>412</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>1,756</td>
<td>75</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>1,394</td>
<td>59</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>4,221</td>
<td>182</td>
</tr>
<tr>
<td>Risperidone</td>
<td>1,566</td>
<td>80</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>697</td>
<td>26</td>
</tr>
</tbody>
</table>

Abbreviation: AP, antipsychotic.

* Cell sizes of 10 or less have been suppressed in accordance with the Centers for Medicare & Medicaid Services cell size suppression policy.

Huybrechts KF et al. JAMA Psychiatry 2016; in press.
Antipsychotics: adverse neonatal events

- Both typical and atypical APDs have been associated with perinatal complications
  - Extrapyramidal signs
  - Agitation, irritability (or sedation)
  - Respiratory distress
  - Tachycardia
  - Feeding difficulties
  - Low blood pressure
  - Functional bowel obstruction


[Link to Newport's study]

[Link to FDA information on drug safety]
FDA Drug Safety Communication: Antipsychotic drug labels updated on use during pregnancy and risk of abnormal muscle movements and withdrawal symptoms in newborns

Safety Announcement

[2-22-2011] The U.S. Food and Drug Administration (FDA) is informing healthcare professionals that it has updated the Pregnancy section of drug labels for the entire class of antipsychotic drugs. The new drug labels now contain more and consistent information about the potential risk for abnormal muscle movements (extrapyramidal signs or EPS) and withdrawal symptoms in newborns whose mothers were treated with these drugs during the third trimester of pregnancy.

Antipsychotics: other reported outcomes

- Large for gestational age (LGA) – Newham, 2008
  - Higher rates of LGE with atypical APD’s (20%) than with typical APD’s (2%) or no APD’s (3%)
  - Olanzapine and clozapine use was associated with higher mean birth weight

- Gestational diabetes (GDM) – Boden, 2012
  - Excluding olanzapine and clozapine, OR 1.8 (95% CI 1.04 to 3.03)
  - Olanzapine and clozapine, OR 1.9 (95% CI 0.97 to 3.91)
Antipsychotic D/C in pregnancy


- 495,953 pregnancies, 365,138 women

- Pregnant and non-pregnant women D/C APDs at same rate up to start of pregnancy

- ATYPs – after 6 weeks of pregnancy, only 54% got further prescriptions; by start of third trimester, this reduced to 38%

- TYPs – after 6 weeks of pregnancy, 35% got further prescriptions; by start of third trimester, this reduced to 19%
Atypical APDs: lactational safety

- Excretion in breast milk
  - Excreted at varying but low levels in breast milk (risperidone, olanzapine, quetiapine)
  - One report suggests clozapine is concentrated in breast milk

- Reported adverse effects in nursing offspring
  - No observed AE’s: risperidone, ziprasidone, aripiprazole, asenapine, lurasidone
  - Olanzapine: cases of somnolence, jaundice
  - Quetiapine: case of mild developmental delay

- Consensus and opinion
  - American Academy of Pediatrics: effects unknown but may be of concern (clozapine); most others unrated
  - Lack of safety data have led some to recommend avoiding breastfeeding while taking antipsychotics
## Selected pregnancy exposure registries in the U.S.

<table>
<thead>
<tr>
<th>Drug/class</th>
<th>Registry</th>
<th>Contact</th>
</tr>
</thead>
</table>
| Atypical APD’s (incl. clozapine) | National Pregnancy Registry for MH Disorders       | Website: [www.womensmentalhealth.org](http://www.womensmentalhealth.org)  
|                             |                                                      | Phone: 1-866-961-2388                                           |
| AED’s                       | Antiepileptic Drug Pregnancy Registry               | Website: [www.massgeneral.org/aed/](http://www.massgeneral.org/aed/)  
|                             |                                                      | Phone: 1-888-233-2334                                           |
| Armodafinil                 | Nuvigil Pregnancy Registry                          | Website: [http://www.nuvigilpregnancyregistry.com/](http://www.nuvigilpregnancyregistry.com/)  
|                             |                                                      | Phone: 1-866-404-4106                                           |
| Duloxetine                  | Cymbalta Pregnancy Registry                         | Website: [http://www.cymbaltapregnancyregistry.com/](http://www.cymbaltapregnancyregistry.com/)  
|                             |                                                      | Phone: 866-814-6975                                            |
| Modafinil                   | Provigil Pregnancy Registry                         | Website: [http://provigilpregnancyregistry.com/](http://provigilpregnancyregistry.com/)  
|                             |                                                      | Phone: 1-866-404-4106                                           |
National Pregnancy Registry for Atypical Antipsychotics (NPRAA)

- Started at MGH in 2008
- 18-45 year old mother
- Three telephone interviews:
  - (a) enrollment
  - (b) 7 months gestation
  - (c) 2-3 months postpartum
- Exposed and non-exposed comparison group
- Medical release authorization: obstetrical, L/D, newborn/peds (up to 6 mo)
- Case confirmed by blinded review

Initial data from NPRAA

December 2014 – N=487 women (353 exposed, 134 controls)
N=303 women with complete data (included in analyses)
N=214 live births with first trim. AAPD exposure; N=89 controls

Mean age 32.3 years; mean baseline BMI 27.1 kg/m²
69% on polytherapy (30% SSRIs, 34% AEDs, 20% anxiolytics)

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Prev (%)</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>First trim. AAPD exposure</td>
<td>3</td>
<td>1.4</td>
<td>1.25</td>
<td>0.13-12.19</td>
</tr>
<tr>
<td>Unexposed to AAPD</td>
<td>1</td>
<td>1.1</td>
<td>Ref.</td>
<td>Ref.</td>
</tr>
</tbody>
</table>

Resources

• www.motherisk.org (1-877-439-2744)
• www.reprotox.org
• www.womensmentalhealth.org (MGH Center for Women’s Health)
• www.marchofdimes.com
• www.postpartum.net (Postpartum Support International)
• www.OTISpregnancy.org (Organization of Teratology Information Services)
• www.mayoclinic.com
Learning Objectives

• Review epidemiology pertinent to bipolar disorder and pregnancy

• Review use of common classes of medications used during treatment of bipolar disorder during pregnancy and lactation:
  • Lithium
  • Anti-epileptic drugs
  • Antipsychotic medications
Questions & Discussion