Bipolar Disorder in Women: Considerations across the Reproductive Lifespan

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  – Dr. Freeman will be discussing off-label use and/or investigational use of prescription medications/medical devices in the presentation and will identify those issues.

• Applicable CME staff have no relationships to disclose relating to the subject matter of this activity.
• This activity has been independently reviewed for balance.
Questions to Keep in Mind

• Does she have a bipolar spectrum disorder?
• Might this patient become pregnant during her treatment?
• What are the risks of the mood stabilizer(s) to a baby (*in utero*, breastfeeding)?
• What are the implications of reproductive events—pregnancy, postpartum, menstrual cycle, perimenopause?
Does She Have a Bipolar Disorder?

- Bipolar disorder is often a missed diagnosis
- Women often present with bipolar depression—need to take careful history to assess for bipolar disorder
- Hypomania may be easy to overlook
Bipolar Disorders across the Female Reproductive Lifespan

- General considerations
- Menstrual cycle
- Pregnancy
- Postpartum
- Menopause
Bipolar Disorder: Sex Differences
Bipolar Disorders in Women

Women experience …

• More rapid cycling
• More mixed episodes
• More depressive symptoms
• Later age of onset
• More bipolar II
• More medical and psychiatric comorbidity
• Higher rates of obesity

Treatment Response

- No evident gender difference in response to mood stabilizers
- More antidepressant-induced rapid cycling
- Differences in side effects
  - eg, Lithium treatment
    - More hypothyroidism and weight gain in women

Menstrual Cycle

• May be exacerbation of symptoms premenstrually or menstrually for some women
  • Case reports, retrospective data
  • Up to 66% reported regularly occurring exacerbations
  • 25% reported premenstrual depressive syndrome, increased anxiety
• Prospective studies: Inconsistent findings
• Medications for PMDD may precipitate mania – mood stabilize first
• Poorer outcomes in women with prospectively documented PMDD based on DSM-5 criteria and bipolar disorder

PMDD = premenstrual dysphoric disorder.

Mood Stabilizers and Menstrual Cycles

- Disruptions in menstrual cycles
  - Valproic acid
    - Associated with PCOS
  - Hyperprolactinemia
    - Galactorrhea, irregular menses/amenorrhea, infertility, sexual dysfunction

PCOS = polycystic ovarian syndrome.
Bone Health and Bipolar Disorder

• Mood disorders and schizophrenia have been associated with low BMD
• May be due to the disorders and/or medications
• **Hyperprolactinemia associated with bone loss**
  – Hyperprolactinemia may cause hypogonadism
  – The presence/duration of low estrogen (and testosterone) appears responsible for bone loss
  – In women with regular menses, hyperprolactinemia not associated with low BMD
  – Especially concerning in young women who require adequate estrogen production for development of adult bone mass

BMD = bone mineral density.
Bone Health and Bipolar Disorder (cont’d)

• Clinical indicators of hyperprolactinemia
  – Galactorrhea
  – Menstrual irregularities or amenorrhea
  – Not a risk factor for osteoporosis without hypogonadism
  – Most likely with older antipsychotics, risperidone
What should we do if we suspect low BMD?

• BMD evaluations: DXA (dual-energy X-ray absorptiometry)
• Ask about menstrual cycle (hypogonadal amenorrhea)
• Smoking increases risk of low BMD
• Calcium supplementation?
  – Bone health (1000–1500 mg/day)
  – May have beneficial mood effects (PMS data)
  – But not at the same time as a thyroid medication – reduced availability of thyroxine with calcium
  – There may be some specific risks with supplements vs dietary intake
    • Calcium monotherapy supplementation (> 1000 mg) may increase risk of stroke, may be offset by co-administration of Vitamin D
    • Supplementation may increase the risk of coronary artery calcification

PMS = premenstrual syndrome.
Pregnancy and Postpartum
Treating Women of Childbearing Potential

- 49% of pregnancies in the United States are unintended
- 80% of teen pregnancies unintended
- 82% of US women have had a child by age 40

CDC Recommendations for Women of Reproductive Age

- Take folic acid
- Maintain healthy diet and weight
- Regular physical activity
- Quit/abstain from tobacco use, alcohol, and drugs
- Communicate with health care providers about screening and management of chronic diseases
- Use effective contraception correctly if one is sexually active and wishing to delay/avoid pregnancy

Context for Assessing Risk

- Rate of major malformations: 3% to 4%
- Rate of premature delivery: 11% to 12%
- Rate of gestational diabetes: 2% to 7%
- Untreated psychiatric disorders carry risks for woman and baby
- Alcohol and tobacco use prevalent in patients with untreated psychiatric disorders
- Obesity increases obstetrical risks
- Older age increases risk

Risks of Untreated Bipolar Disorder during Pregnancy

- > 330,000 women; included comparisons of women with bipolar disorder, with and without treatment
  - Bipolar disorder increases risk of
    - C-section
    - Small for gestational age
    - Prematurity
  - Congenital malformations
    - Without bipolar disorder: 2.0%; untreated 1.9%
    - 3.4% treated with a mood stabilizer (lithium or anticonvulsant)

Depression during Pregnancy

FDA Ratings
A: Studies in humans show no risk
B: No evidence risk in humans; if no human data, animal data show no risk
C: Risk cannot be ruled out
D: Positive evidence of risk
X: Contraindicated in pregnancy

NOT HELPFUL OVERALL
Transitioning out of use

Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products — Content and Format Guidance for Industry

DRAFT GUIDANCE

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologic Evaluation and Research (CBER)

December 2014
Labeling
The Pregnancy and Lactation Labeling Rule (PLLR) or “Final Rule”

Subsections
- Pregnancy
- Lactation
- Females and Males of Reproductive Potential

Pregnancy Exposure Registry
- Scientifically acceptable registry and contact info

Risk Summary
- Human, animal, pharmacologic data
- Adverse developmental outcomes
  - Structural abnormalities, embryo-fetal and/or infant mortality, functional impairment, alterations to growth
- Background risks from the US population (ie, CDC data)

Context
- Includes information about background rates of adverse events
- Risks to be quantitatively compared to the risk for the same outcome in infants born to women not exposed to the drug, but who have the disease or condition for which the drug is indicated (ie, appropriate controls)

APA/ACOG Joint Recommendations

• Psychotherapy: First-line for mild to moderate MDD
• **Lifestyle components**: Nutrition, weight management, prenatal care, childbirth education; treatment for substance abuse
• **Women trying to conceive who have histories of MDD**
  – Encourage period of euthymia
  – Sustained remission: May consider tapering and discontinuing
  – More recently depressed or with symptoms: Consider remaining on medication, optimizing medication
• **Pregnant women with severe MDD**: Medication is first-line
• **Pregnant women on antidepressants during pregnancy**: Take into account patient preferences, previous course of illness
• Medication selection should be based on known safety information

Psychotropics and Pregnancy: Overview and Controversies

Breastfeeding

• …The experience of breastfeeding is special for so many reasons – the joyful bonding with your baby, the cost savings, and the health benefits for both mother and baby…

• …Time to declare an end to the breastfeeding dictatorship that is drowning women in guilt and worry just when they most need support...

Pregnancy and Postpartum: 
*Risks of Discontinuing Medication*

- Retrospective and prospective data show mean rates of relapse during pregnancy between 55% to 70%
- Women who discontinue medication more likely to experience recurrences (85.5% vs 37%) and spend more time ill
- Particularly high rate of mood episodes postpartum (70%)
- Recurrence risk greater after rapid discontinuation (< 2 weeks) than gradual (2 to 4 weeks)
- Unplanned pregnancy associated with greater risk of recurrence

Highest risk of hospitalization for new mothers is 10 to 19 days postpartum, increased outpatient contacts first 3 months

Postpartum Psychosis
Postpartum Psychosis

• 1 to 2 per 1000 pregnancies
• Rapid, dramatic onset within first 2 weeks
• High risk of harm to self and infant
• Suspect bipolar disorder
  – Underlying diagnosis: Affective psychosis (bipolar disorder or schizoaffective disorder)
  – Family and genetic studies, index episode follow-up
Postpartum Psychosis (cont’d)

- Psychiatric emergency
- Estimated that 4% of women with postpartum psychosis commit infanticide
  - Actual rates of infanticide are difficult to estimate, as infanticide may be underreported

# Risk Factors for Postpartum Psychosis

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>% that Developed Postpartum Psychosis</th>
</tr>
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<tbody>
<tr>
<td>Hospitalization for psychotic episode during the pregnancy</td>
<td>44%</td>
</tr>
<tr>
<td>Hospitalization for a psychotic episode prior to the pregnancy</td>
<td>14.5%</td>
</tr>
<tr>
<td>Any previous psychiatric hospitalization</td>
<td>9.2%</td>
</tr>
<tr>
<td>Previous hospitalization for bipolar mood episode</td>
<td>2.0%</td>
</tr>
<tr>
<td>Baseline population risk</td>
<td>0.07%</td>
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</table>

Acute Treatment

- Inpatient psychiatric hospitalization
- Rule out medical conditions
- Length of stay depends on clinical condition
- Many women will need to stop breastfeeding
- Primary pharmacotherapy: Mood stabilizer and an antipsychotic, with medications for anxiety, insomnia, and agitation as needed
  - Sequential use of benzodiazepines, antipsychotics, lithium, and ECT proposed

ECT = electroconvulsive therapy.
Acute Treatment (cont’d)

• Inpatient Protocol – Sequential use: N=64
  – **Step 1**: Benzodiazepine (lorazepam), 3 days – 6% remitted (n=4)
  – **Step 2**: Antipsychotic: haloperidol or atypical – 19% remitted (n=12)
  – **Step 3**: Lithium – 73% remitted (n=48)
  – **Step 4**: ECT – none underwent
  – Total of 98% remission; only 1 patient did not fully remit
    • Most women responded to by addition of lithium
  – Sustained remission at 9 months postpartum in 80%
    • Affective diagnosis more associated with remission than non-affective
    • Relapse rates higher with antipsychotics than with lithium

Treatment after Discharge

• Little data to inform length of care
  – 6 to 12 months of pharmacotherapy
  – Psychotherapy and close monitoring
• Treatment planning for adequate sleep, support, help in meeting the needs of caring for a baby
• Close monitoring is required for safety
  – Psychoeducation of family and friends
Significant difference between groups (Peto-Peto-Wilcoxon $\chi^2 = 6.966, df = 1, P<.01$).
Postpartum Relapse: Bipolar Disorder

Pharmacotherapy strongly influences rate of relapse
Prevention of Postpartum Psychosis

- Are outcomes different in women who have only had postpartum psychotic episodes and no other mood episodes?
- When should medication prophylaxis be initiated?
  - Most using lithium
  - Advised to use lithium prophylaxis immediately after delivery
### Prevention of Postpartum Bipolar Episodes and Postpartum Psychosis


<table>
<thead>
<tr>
<th>Group</th>
<th>During Pregnancy</th>
<th>With Postpartum Prophylaxis</th>
<th>Did NOT Start Postpartum Prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women with histories of psychosis in the postpartum only</td>
<td>All (29/29) remained stable off of medication during pregnancy</td>
<td>No relapses (N=20)</td>
<td>44% relapse (N=9)</td>
</tr>
</tbody>
</table>
| Women with bipolar disorder                               | 24.4% relapse: 75.6% on maintenance medications Relapse rates:  
  • 19.4% on medications  
  • 40% off medications  | Of those who stayed well during pregnancy: Postpartum relapse rate 7.7%  | Of those who stayed well during pregnancy: Postpartum relapse rate 20%  | 60% postpartum relapse among those who experienced mood episodes during pregnancy |
Main Points

• History of isolated postpartum psychosis
  – High risk for recurrence postpartum
  – Prophylaxis may be deferred to immediately postpartum if mother well throughout pregnancy

• Bipolar disorder
  – **High risk for recurrence throughout pregnancy and the postpartum**, particularly with medication discontinuation
  – High risk postpartum relapse, postpartum prophylaxis decreases risk
  – Clinical picture during pregnancy greatly factors into postpartum prognosis – do not delay treatment

Postpartum Treatment

- **Prescribe Sleep!**
  - Sleep deprivation – similar to antidepressants regarding risk of induction of mania/hypomania (10%)

- **Prescribe Support!**
  - Good social support associated with quicker recovery, less symptomatic; better prophylaxis against episodes

Differentiating OCD and Psychosis

**Postpartum OCD**
- Thoughts are ego-dystonic
- Disturbed by thoughts
- Avoid objects or being with their newborn
- Very common disorder
- Low risk of harm to baby

**Postpartum Psychosis**
- Thoughts are ego-syntonic
- May not be distressed by thoughts
- May not show avoidant behaviors
- Not common disorder
- High risk of harm to baby

OCD = obsessive-compulsive disorder.
Mood Stabilizers in Pregnancy

• Lithium: First-trimester risk of cardiovascular malformations
  – Ebstein’s anomaly: 0.1% to 0.2% (RR = 10–20)
  – RR for cardiac malformations is 1.2 to 7.7 and the risk for Ebstein’s anomaly rises from 1/20,000 to 1/1000

• Lithium
  – Complicated by maternal GFR changes during pregnancy. Excreted more rapidly—may need to increase dose
  – After delivery, GFR decreases rapidly, should follow lithium levels during labor and delivery, adjust dose as needed

RR = risk ratio; GFR = glomerular filtration rate.
Valproic Acid

- **Worst Teratogen Known Among Psychotropics**
  - Rate of major malformations: $\geq 10\%$
    - Neural tube defects, craniofacial, cardiovascular, and others
    - Risk of defects is substantial in very early pregnancy
  - Associated with increased risk for adverse cognitive and neurodevelopmental effects
    - Long-term follow-up (up to 3 years) suggests fetal exposure to valproate associated with lower IQ scores (not observed with lamotrigine)

IQ Scores of Children at 3 Years of Age According to *In Utero* Exposure to Antiepileptic Drugs

<table>
<thead>
<tr>
<th>Variable</th>
<th>Carbamazepine (N=73)</th>
<th>Lamotrigine (N=84)</th>
<th>Phenytoin (N=48)</th>
<th>Valproate (N=53)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean IQ (95% CI)†</td>
<td>98 (95–102)</td>
<td>101 (98–104)</td>
<td>99 (94–104)</td>
<td>92 (88–97)</td>
</tr>
<tr>
<td>Mean difference in IQ from valproate group (95% CI)‡</td>
<td>6 (0.6–12.0)</td>
<td>9 (3.1–14.6)</td>
<td>7 (0.2–14.0)</td>
<td></td>
</tr>
<tr>
<td>P-value§</td>
<td>0.04</td>
<td>0.009</td>
<td>0.04</td>
<td></td>
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</table>

* The results are based on regression models for the intention-to-treat population (309 children). See Table 1 in the Supplementary Appendix for full results of the regression models. IQ at 3 years of age was imputed for 77 of the original 309 children born alive who were not assessed at that age (1 of these children died from severe heart malformation, 6 were enrolled in the NEAD study from the United Kingdom study after they had reached 3 years of age, 31 withdrew before 3 years of age, and 39 did not present for testing).

† Least-squares means from the primary analysis are given after adjustment for maternal IQ and age, antiepileptic-drug dose, infant’s gestational age at birth, and maternal preconception use of folate.

‡ Although the confidence intervals for carbamazepine and phenytoin overlap with the confidence interval for valproate, the confidence intervals for the differences between carbamazepine and valproate and between phenytoin and valproate do not include zero.

§ P values are for the comparison with the valproate group. P values from tests of the null hypothesis of no difference from the valproate-group mean were adjusted for multiple comparisons.23

Lamotrigine in Pregnancy

• No increased risk of major malformations
• Association with oral clefting NOT seen with larger numbers
  – Early data suggested it might be when numbers were smaller
  – Recent large study of registries did not find any association between oral clefts and lamotrigine
• Pregnancy increases lamotrigine clearance by > 50%
  – Returns to baseline after delivery

Atypical Antipsychotics in Pregnancy

- **Large administrative Medicaid database**
  - Nationwide sample of N=1,360,101 pregnant women
  - After confounding adjustment, the RR was reduced to 1.05 (95% CI, 0.96–1.16) for atypical APs and 0.90 (95% CI, 0.62–1.31) for typical APs. The findings for cardiac malformations were similar
  - For the individual agents examined, a small increased risk in overall malformations (RR, 1.26; 95% CI, 1.02–1.56) and cardiac malformations (RR, 1.26; 95% CI, 0.88–1.81) was found for risperidone that was independent of measured confounders

- **Pooled odds ratios of prospective studies**
  - AP exposure associated with slightly increased risk of major malformations, heart defects, preterm delivery, small-for-gestational-age births, decreased birth weight
  - There was no significant difference in the risk of major malformations differences between typical (and atypical) AP medications

AP = antipsychotic.
National Pregnancy Registry for Atypical Antipsychotics

- Research study at the Massachusetts General Hospital Center for Women’s Mental Health
- To determine the safety of atypical antipsychotics in pregnancy for women and their babies
- Participation will involve 3 brief phone interviews over approximately 8 months

Call toll-free: 1-866-961-2388
National Pregnancy Registry for Atypical Antipsychotics

• Now > 1100 patients have been enrolled!

Early Data
• As of December 2014, N=487 enrolled
• N=303 eligible for analyses
• Rates of major malformations in the 2 groups similar
  – 1.4% (3/214 live births) in exposed group
  – 1.1% (1/89) in the comparison group
  – Odds ratio for major malformations comparing exposed infants with unexposed infants was 1.25 (95% CI = 0.13–12.19) – not statistically significant

Benzodiazepines and Pregnancy

- Benzodiazepines are lipophilic and undergo rapid fetal transfer and uptake
- First trimester exposure: Inconsistent findings of association with cleft palate or other congenital abnormalities
- Late pregnancy exposure: Possible withdrawal, neonatal sedation, hypotonia, cyanosis
- Avoidance in the first trimester, avoidance of polypharmacy suggested
Mood Stabilizers and Breastfeeding

- Lithium
  - Toxicity reported in cases with infant serum levels at 0.1 to 0.5 × the maternal level
  - Contraindicated at one time by the American Academy of Pediatrics
    - Revised to classification “Drugs That Have Been Associated With Significant Effects on Some Nursing Infants and Should Be Given to Nursing Mothers With Caution”

Mood Stabilizers and Breastfeeding (cont’d)

**Lithium and Breastfeeding**
- N=10 mother-baby pairs
- Mothers stable, lithium monotherapy 600 to 1200 mg/day
- Babies’ serum levels 0.09 to 0.3 meq/L (average 0.16)
- Transient increases in elevated infant TSH, BUN, Cr

**Recommendations**—Consider lithium when
1. Bipolar disorder in mother who is stable
2. Lithium monotherapy (or simple regimen)
3. Adherence to infant monitoring (lithium level, TSH, BUN, Cr immediately postpartum, 4 to 6 weeks of age, and then every 8 to 12 weeks)
4. Healthy infant
5. Collaborative pediatrician

BUN = blood urea nitrogen; Cr = creatinine; TSH = thyroid-stimulating hormone.

Menopause

• Very sparse data
• There may be mood worsening associated with the menopausal transition, particularly depressive episodes and symptoms

Thank you!

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