Management of Peripartum Mental Health Matters – Workshop

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Faculty/Presenter Disclosure

- Faculty: Verinder Sharma
- Relationships with commercial interests:
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  - Speakers Bureau/Honoraria: Neuroscience Education Institute
  - Consulting Fees: Otsuka, Sunovion Pharmaceuticals
Learning Objectives

• Understand the effect of pregnancy and childbirth on the course of bipolar disorder

• Implement safe and effective strategies to manage bipolar disorder during and after pregnancy
DSM-5 Classification

- Disruptive mood dysregulation disorder
- Major depressive disorder (MDD)
- Persistent depressive disorder
- Premenstrual dysphoric disorder
- Substance/medication-induced depressive disorder
- Depressive disorder due to another medical condition
- Other specified depressive disorder
- Unspecified depressive disorder
- Bipolar I Disorder (BD-I)
- Bipolar II Disorder (BD-II)
- Cyclothymic disorder
- Other specified bipolar and related disorder
- Unspecified bipolar and related disorder
- Substance/medication-induced bipolar disorder
- Bipolar disorder associated with a known medical condition

American Psychiatric Association (2013). Diagnostic and statistical manual of mental disorders (5th ed.)
Bipolar Disorder Subtypes

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Spectrum of Bipolar Disorder

Divided according to severity of mood elevation during acute episodes

**BD-I**

Threshold mania
- Inflated self-esteem
- Decreased need for sleep
- Pressured speech
- Racing thoughts
- Distractibility
- Psychomotor agitation
- Risky behaviour
- ± psychotic features
- ± hospitalization

**BD-II**

Hypomania
- Qualitatively similar to mania but insufficient duration or severity to cause significant impairment, hospitalization or psychosis
- Includes threshold depressive episodes

**Cyclothymia**

Threshold hypomania and depression
- Chronic symptoms
- Not meeting criteria for major depressive or manic/hypomaniac episode

DSM-5 Criteria for a Major Depressive Episode (MDE)

A minimum of 2 weeks of depressed mood and/or anhedonia and at least 4 other symptoms including changes in:

- Sleep
- Appetite/weight
- Energy
- Psychomotor activity
- Concentration
- Thought content (guilt, worthlessness)
- Suicidal intent

American Psychiatric Association (2013). Diagnostic and statistical manual of mental disorders (5th ed.)
# DSM-5 Specifiers for Bipolar and Related Disorders

<table>
<thead>
<tr>
<th>Specifier</th>
<th>Manic Episode</th>
<th>Depressive Episode</th>
<th>Illness Course</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxious Distress</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Mixed Features</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Rapid Cycling</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Melancholic Features</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Atypical Features</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Psychotic Features</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Catatonia</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Peripartum Onset</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Seasonal Pattern</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Remission</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Current Episode Severity</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>

Adapted from: American Psychiatric Association (2013) Diagnostic and statistical manual of mental disorders (5th ed.)
Gender Differences

- Women are **more** likely to have
  - rapid cycling,
  - mixed and dysphoric mania
  - seasonal pattern
  - longer depressive episodes
  - bipolar II disorder comorbidity with medical disorders (e.g. thyroid disease, migraine, obesity), and anxiety disorders
- **Less** substance abuse, and completed suicides
- Gender does not affect response to MS drugs, however, women are more likely to have delayed diagnosis and treatment

Reproductive Events and BD

• Menarche
  • In 1/3 of cases onset of BD was within one year of menarche

• Menstrual Period
  • PME – 64-68% of women in retrospective Studies; 44-65% of women in prospective studies
  • PMS – 25-77%
  • PMDD – 15-27%

• Menopause
  • ↑ proportion of clinic visits with depressive symptoms compared to similarly aged men, and younger women and men with BD

Treatment Considerations

- Discussion regarding reproductive planning for women considering pregnancy; referral for contraceptive advice
- Pre-pregnancy consultation should be encouraged for women who plan to pursue pregnancy
- **Valproate should not be prescribed**
  - Women taking carbamazepine (CBZ), topiramate (TPM), or lamotrigine (LTG) who are using oral contraceptive pills (OCPs) should be informed of the potential for decreased effectiveness of OCPs and increased risk of unplanned pregnancies
- Typical antipsychotics and risperidone may interfere with ovulation

Pre-pregnancy Counselling

- Pre-pregnancy consultation (3 months prior for patients considering pregnancy or immediately for those who have recently become pregnant)
  - Decreased risk of recurrence during pregnancy in women who had a prolonged period of mood stability prior to pregnancy (duration)
- Effect of pregnancy and the postpartum period on the illness course
- Providing accurate and balanced information about treatment options, relative risks, and the limits of current knowledge
- Genetic transmission

Effect of Pre-pregnancy Counselling

- Follow-up survey of women seen at the Massachusetts General Hospital after specialized consultation about their family planning decisions
  - 45% had been advised to avoid pregnancy by a health care professional before consultation (69% by a mental health professional)
  - After consultation, 63% decided to pursue pregnancy
- Common reasons for avoidance of pregnancy
  - Teratogenic risks – 56%, risk of recurrence after medication discontinued – 50%, potential genetic transmission – 22%, reluctance to repeat previous pregnancy-associated illness – 17%, and fear that recurring mood episode would adversely affect a fetus or existing children – 17%

Pre-pregnancy Counselling

- Women who are **clinically stable for 4 to 6 months and are at low risk for relapse** can have their mood stabilizer (MS) tapered off prior to pregnancy (BC-CAN).

- **Women taking valproate** prior to pregnancy should be switched to a different psychotropic agent—continually assess re-emergence of mood symptoms.

- Lithium should not be used during pregnancy unless other antipsychotic medications have been ineffective, and a discussion about the risk/benefit ratio of medication use has occurred (SIGN).

- Specialist input, pre-pregnancy management plan.
How Common is BD in Pregnancy?

- Among 274 participants, 14 (5.1%) were positive.
  - Prevalence of positive screens for BD in an obstetric population is similar to gestational diabetes and hypertension, which are screened for routinely.

- 12% of women referred to a women’s mental health program for psychiatric assessment during pregnancy.

- No published studies on the first-time onset of hypomania or mania or how frequently BD begins with a depressive episode during pregnancy.
Effect of Lithium Discontinuation

Mood Episodes During and After Pregnancy

<table>
<thead>
<tr>
<th>Group and Clinical Type</th>
<th>During Pregnancy</th>
<th>During Postpartum Period</th>
</tr>
</thead>
<tbody>
<tr>
<td>BD-I (N=479)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major depression</td>
<td>8.88</td>
<td>19.21</td>
</tr>
<tr>
<td>Mania</td>
<td>2.32</td>
<td>7.93</td>
</tr>
<tr>
<td>Hypomania</td>
<td>2.70</td>
<td>1.25</td>
</tr>
<tr>
<td>Mixed states</td>
<td>8.11</td>
<td>6.47</td>
</tr>
<tr>
<td>Anxiety or panic</td>
<td>1.54</td>
<td>1.25</td>
</tr>
<tr>
<td>Psychosis</td>
<td>1.16</td>
<td>1.88</td>
</tr>
<tr>
<td>All episodes</td>
<td>24.71</td>
<td>37.99</td>
</tr>
</tbody>
</table>

# Bipolar Mood Episodes During and After Pregnancy

<table>
<thead>
<tr>
<th>Group and Clinical Type</th>
<th>During Pregnancy</th>
<th>During Postpartum Period</th>
</tr>
</thead>
<tbody>
<tr>
<td>BD-II (N=641)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major depression</td>
<td>10.36</td>
<td>28.71</td>
</tr>
<tr>
<td>Hypomania</td>
<td>2.79</td>
<td>2.34</td>
</tr>
<tr>
<td>Mixed states</td>
<td>3.59</td>
<td>2.50</td>
</tr>
<tr>
<td>Anxiety or panic</td>
<td>3.59</td>
<td>0.94</td>
</tr>
<tr>
<td>Psychosis</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>All episodes</td>
<td><strong>20.37</strong></td>
<td><strong>34.49</strong></td>
</tr>
</tbody>
</table>

Recurrence Risk: A Prospective Study

- A prospective observational clinical cohort study
- 89 pregnant women with DSM-IV BD
- Eligible subjects were euthymic at conception and continued MS or discontinued treatment proximate to conception
- Overall risk of at least one recurrence in pregnancy was 71% (74% depressive or mixed: 47% in first trimester)
- Among those who discontinued MS:
  - recurrence risk was 2-fold greater
  - median time to first recurrence was more than 4-fold shorter
  - proportion of weeks ill during pregnancy was 5 times greater

Pregnancy and BD

• Depressive/mixed episodes are more common than hypomanic/manic episodes
• Episodes more frequent following abrupt discontinuation of MS
• Clustering of episodes during the first trimester (? medication withdrawal)
• All recurrences in the third trimester (last 5 weeks) in unmedicated women

Grof et al. JAD,2000;6; 31-9.
Antidepressant Discontinuation Syndrome

• Remembering the discontinuation syndrome acronym FINISH
  • Flu-like symptoms,
  • Insomnia,
  • Nausea,
  • Imbalance,
  • Sensory disturbances,
  • Hyperarousal (anxiety/agitation)

Does Pregnancy Have a Positive Effect on BD?
Reduced Risk of Hospitalization in Pregnancy

Neutral Effect of Pregnancy on BD

Methodological Limitations of Studies of BD During Pregnancy

**Key Limitations:**

- Focus on women assessed at specialty clinics
- Exclusion of women who were not on psychotropic medications
- Difficulty differentiating between the effects of medications from the effect of pregnancy on the illness course
- Increasing use of antidepressants (ADs) and ensuing mood instability may be obscuring the positive effect of pregnancy
- Retrospective versus prospective methods
- Non-reporting of potential confounds such as parity status and psychiatric comorbidity
Effect of Pregnancy on BD

• A total of 70 articles were identified and included in the review

• Evidence from studies using nonclinical samples, some retrospective studies, and studies on psychiatric hospitalization rates is suggestive of a positive effect of pregnancy on bipolar disorder

• “Resolution of this uncertainty will require well-matched—and, ideally, prospective—comparisons of episode occurrence rates and exposure times during pregnancy compared with periods unrelated to pregnancy”

Self Harm in Pregnancy

• Historical cohort study from UK (2007-2011), affective and non-affective psychoses

• Of 420 women, 24.5 % had a record of SI during the index pregnancy, with self-harm recorded in 7.9 %

• 52 events of self harm (1 in 19 women)
  • Overdose (38.5 %), hitting (23.1 %), cutting (17.3 %) or a violent method (21.2 %) such as jumping from height, burning or hanging

  • 43.1 % events while experiencing hallucinations and 34.6 % had use drugs or alcohol 12 h before the self-harm

• Self harm was independently associated with: younger age, self-harm in the previous 2 years and smoking

Balancing of Risks

↑ risk of mood episodes versus ↑ risk of potential congenital malformations and perinatal complications
Risks of Adverse Pregnancy and Birth Outcomes

- Women with a record of at least two bipolar diagnoses were grouped as **treated** (those who had filled a prescription for MS during pregnancy) or **untreated**
- Both groups were compared with all other women giving birth
- Women with BD, regardless of treatment with MS, were at an increased risk of
  - delivering a preterm infant (<37 weeks gestation)
  - microcephaly
  - neonatal hypoglycaemia
- Mechanisms
  - higher psychosocial stress---higher serum cortisol levels
  - Comorbidity and lifestyle issues--overweight, smokers, and an alcohol or substance use disorder (SUD)

Bodén, R, BMJ 2012;345:e7085 doi: https://doi.org/10.1136/bmj.e7085
Perinatal Outcomes Among Women with BD

- Population-based cohort study of women with a singleton delivery in Ontario, Canada (2003-2011). Women previously hospitalized for BD (n = 1859) were compared to women without a documented mental illness.
- BD was associated with
  - preterm birth, severe large for gestational age (>90\textsuperscript{th} percentile), higher risk of congenital malformations, neonatal morbidity, and neonatal hospital readmission.
- Attention to potentially modifiable risk factors such as obesity, DM, and HT before and during pregnancy could reduce the risk for adverse perinatal outcomes.

Infants of Mothers With BD: One-Year Developmental Outcomes

- Outcome of 15 children who were exposed to lithium in utero and were not breastfed were tested at 3-15 years.
- Neurological screening and growth measurements did not show significant abnormalities in the children.
- Motor and behavioural development showed no significant abnormalities, based on the Child Behavior Checklist and developmental questionnaire.
- Intelligence tests detected lower scores in the performance tests in nearly all children, but the difference with a control general population was not significant.

Long-Term Neurodevelopmental Effects

• Preclinical studies suggest a harmful effect of lithium and neuroleptics on motor activity, developmental milestones and reflexes, spatial memory and brain weight
• Transient delay in motor functioning in children with in utero exposure to neuroleptics
• Only 3 clinical studies on in utero exposure to lithium; all reported normal development

## Lithium

<table>
<thead>
<tr>
<th>Medication</th>
<th>Risk of Congenital Anomalies</th>
<th>Pregnancy Outcomes</th>
</tr>
</thead>
</table>
| Lithium    | • Significant ↑ risk of cardiac anomalies (2.4% versus 1.15% in unexposed group)  
• Ebstein’s anomaly --- (1/1,000 with first trimester exposure versus 1/20,000 in general population)  
• 400 fold increase in original studies versus 20 fold increase  
• Adjusted risk ratios 1.65 overall, dose ≤ 600 mg 1.11, 601-900 mg 1.60, and 3.22 for >900 mg | Significant ↑ risk of miscarriages (OR = 1.94%, 95% CL 1.08-3.48) and elective terminations (9.3% versus 2%) |

# Lamotrigine

<table>
<thead>
<tr>
<th>Medication</th>
<th>Risk of Congenital Anomalies</th>
<th>Pregnancy Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lamotrigine</td>
<td>• No increased rates of congenital anomalies versus disease-matched controls (OR 1.15, 95% CI 0.62-2.16, n = 1412) or total control population (OR 1.25, 95% CI 0.89-1.74, n = 774,571)</td>
<td>• No increase in rates of miscarriages, stillbirths, preterm births, or small for gestational age neonates</td>
</tr>
</tbody>
</table>

# Valproate and Carbamazepine

<table>
<thead>
<tr>
<th>Medication</th>
<th>Risk of Congenital Anomalies</th>
<th>Pregnancy Outcomes</th>
</tr>
</thead>
</table>
| **Valproate** | • Significantly increased rate of congenital anomalies (OR, 2.93; 95% CrI, 2.36-3.69) | • Increased risk of combined fetal loss  
• Risk of prenatal growth retardation was not significant (OR 1.28, 95% CrI 0.86-1.95) |
| **Carbamazepine** | • Significantly increased rate of congenital anomalies (OR 1.37, 95% CrI 1.10-1.71) compared to control pregnancies | • Risk of combined fetal loss (OR 1.25, 95% CrI 0.77-1.67, n=2897) were not significantly different versus control pregnancies |

Reproductive Safety of SGAs

• 303 women-- Massachusetts General Hospital National Pregnancy Registry for Atypical Antipsychotics

• Of 214 live births with first-trimester exposure to second-generation antipsychotics (SGA), **three major malformations** were confirmed (transposition of the great arteries, ventricular septal defect, imperforate hymen) In the control group (N=89), **one major malformation** (midshaft hypospadias) was confirmed

• The **absolute risk of major malformations was 1.4% for exposed infants and 1.1% for unexposed infants.**

WHO Guidelines for Substance Use Disorders

• Advise women dependent on ETOH or drugs to cease their ETOH or drug use and offer, or refer to, detoxification services under medical supervision where necessary and applicable

• Encourage women dependent on opioids to use opioid maintenance treatment (methadone or buprenorphine) whenever available rather than to attempt opioid detoxification

• Women with benzodiazepine (BZD) dependence should undergo a gradual dose reduction, using long-acting BZDs

• Mothers with substance use disorders should be encouraged to breastfeed unless the risks clearly outweigh the benefits

World Health Organization, 2014
Stimulant Use in Pregnancy

- Population-based cohort study of pregnant women and their live born neonates enrolled in Medicaid from 2000 to 2010
- Women who received amphetamine in the first half of pregnancy were compared with unexposed women
- Atomoxetine, a non stimulant ADHD medication, used as a negative control exposure
- Psychostimulant use during pregnancy was associated with a small increased relative risk of pre eclampsia (1.29 for preeclampsia (95% CI 1.11–1.49), and 1.30 for preterm birth (1.10–1.55)
- Effect on course of BD

Marijuana and Pregnancy

- Marijuana use—2-5% self-reported prevalence
- No association with perinatal death but risk of stillbirth may be modestly increased
- Women who are pregnant or contemplating pregnancy should be encouraged to discontinue marijuana use and stop use of marijuana for medicinal purposes in favour of a safe alternative therapy
- Due to insufficient data to evaluate the effects of marijuana use on infants during breastfeeding, marijuana use should be discouraged

ACOG Committee Opinion, Number 722, October 2017.
# Acute or Maintenance Treatment of Antenatal BD

<table>
<thead>
<tr>
<th>Factor to be Considered</th>
<th>Clinical Reasoning</th>
</tr>
</thead>
</table>
| The woman’s treatment preferences                  | • Fetal safety predominant concern  
• Some may accept risks to reduce risk of relapse or to treat acute episodes                                                                    |
| Current time of gestation                           | • Risk of congenital anomalies highest in 1\textsuperscript{st} trimester  
• Risk of neonatal withdrawal and adaptation syndromes highest near delivery                                                                   |
| Fetal safety of medication under consideration      | • Lamotrigine safer to use in pregnancy  
• Others (valproate, carbamazepine) should be used only when all others have failed                                                                   |
| Past illness course                                 | • Helps to estimate likelihood and severity of a relapse                                                                                             |
| History of rapid cycling                            | • Women with rapid cycling experience episodes more frequently, higher likelihood of relapse during pregnancy                                           |

# Acute or Maintenance Treatment of Antenatal BD

<table>
<thead>
<tr>
<th>Factor to be Considered</th>
<th>Clinical Reasoning</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous peripartum mood/psychotic episodes</td>
<td>• Relapse rates are greatly increased in these women</td>
</tr>
</tbody>
</table>
| Past response to MS medications                  | • History of poor response – may not be worth fetal risk  
• History of good response – may be able to quickly recover from relapse if mood stabilizers discontinued |
| Comorbid psychiatric disorders                   | • Women with comorbid disorders at higher risk of relapse  
• Polypharmacy may be needed to treat comorbidities  
• Psychotherapy should be considered where applicable |

## Acute or Maintenance Treatment of Antenatal BD

<table>
<thead>
<tr>
<th>Factor to be Considered</th>
<th>Clinical Reasoning</th>
</tr>
</thead>
<tbody>
<tr>
<td>Access to psychotherapy</td>
<td>• Use of psychotherapy may help reduce risk of relapse in women who taper or discontinue medications during pregnancy</td>
</tr>
<tr>
<td>Lower risk sub-population</td>
<td>• Women with BD-I and a history of robust response to lithium may be at lower risk of relapse during pregnancy</td>
</tr>
</tbody>
</table>
| Strength of social network       | • Women with stronger support networks may be able to tolerate depressive symptoms better  
                          | • Significant relapses may be identified earlier                                      |

Balancing of Risks

FIVE OPTIONS

• No change

• Consider discontinuing medication
  • Mild illness and good protective factors (strong support system, access to follow-up, and history of good response to treatment)

• Selective discontinuation of psychotropic medications
  • Medications deemed least efficacious and those with highest fetal risks
  • Medications not considered concordant with BD treatment guidelines (e.g. antidepressants)
Balancing of Risks (contd.)

• Discontinuing MS during the first trimester with a plan to restart them later in the pregnancy to reduce the risk of teratogenicity
  • May increase the risk of relapse (47% in first trimester)
• Changing maintenance medication to a MS with better safety profile
Maintenance Treatment - Lithium

- NICE has advised against the use of lithium in women who are planning to become pregnant or are pregnant unless antipsychotic medication has not been effective.
- Tapering of lithium during the first trimester could be considered but should be weighed against the risks of relapse.
- There doesn’t seem to be no association between lithium use and pregnancy or delivery related outcomes, but more research is needed.
- Grof study of lithium responsive BD-I low rate of relapse and all relapses were in the last 5 weeks.

Medication Monitoring

- ↑ plasma volume, hepatic activity and renal clearance

**LITHIUM**: anticipate progressively decreasing levels until 17 weeks of gestation, consider bid dosing

- **Pregnancy**- serum level q3 weeks until 34 weeks and then once weekly until delivery
- **After delivery** and twice weekly x 2 weeks
- Consider regular creatinine monitoring

- **AAPs**: monitoring for blood glucose
- Monitoring of neonates (neuroleptic exposure, lithium toxicity, AD withdrawal)

Maintenance Treatment - Lamotrigine

- Effective in the maintenance treatment of BD and acute treatment of bipolar depression
- Relatively positive safety profile; dose adjustment may be needed due to increased renal clearance in pregnancy
- **Newport study** - 26 initially stable women who stayed on LTG or discontinued all MS
  - Antenatal relapse rate of 30% (LTG) versus 100% (MS discontinued)
  - Longer time to relapse in the lamotrigine (LTG) treated women

Maintenance Treatment - Lamotrigine

- Using Danish national registries compared
  - Risk of inpatient psychiatric admission within 3 months postpartum between women with BSD who used LTG (N=55) versus lithium (N=59) during pregnancy

- Rate of postpartum hospitalization 7.3% in LTG treated women versus 15.3% in the lithium group but it did not reach statistical significance

- ADs 72.7% in the LTG group versus 50% in the lithium group

Valproate Prevention of Postpartum BD

• Single-blind, nonrandomized clinical trial (N=26)
• Subjects were enrolled during pregnancy and chose either valproate (VPA) plus symptom monitoring or monitoring without medication
• Mania and depression symptoms were assessed weekly for 20 weeks by an independent evaluator
  • No significant differences between groups in the proportions of women who had mood episodes
    OR
  • time to occurrence of episodes
• Women treated with VPA tended to have lower levels of hypomanic/manic symptoms.

Folic Acid and Spina Bifida

- The U. S. Public Health Service and CDC recommend that all women of childbearing age consume 0.4 mg (400 micrograms) of folic acid daily to prevent spina bifida and anencephaly.

- Standard supplementation of folic acid during pregnancy can reduce risk of spontaneous spina bifida but *not that associated with valproate or carbamazepine*.  

Electroconvulsive Therapy (ECT) in Pregnancy

- SYSTEMATIC REVIEW
  - 169 pregnant women were identified
  - Mean number of 9.4 ECTs
  - Most women received ECT during the 2nd trimester and many were Para I
    - Depression/BD (including psychotic depression) main indications
    - Adverse events such as fetal heart rate reduction, uterine contractions, and premature labour were reported for nearly one third (29%). The overall child mortality rate was 7.1%.
    - ECT during pregnancy should be used as a last resort treatment under very stringent diagnostic and clinical indications

Effect of Drug Treatment

- A prospective naturalistic study of 88 treated and 64 untreated women
- Among the 88 women treated, 23 (26%) discontinued their medication in the first trimester
- More than two-thirds (73%) of the women who remained in the study took psychotropic agents postpartum
  - 66% received a guideline-concordant drug, and 34% received either AD (for BD-I) or mono- or polypharmacy with a variety of other agents
- Mean scores of depression were in the mild range in both the treated and untreated groups in both pregnancy and postpartum
- The majority of women had no or few symptoms of mania

Postpartum Period
Postpartum Psychiatric Disorders

- Baby blues, postpartum depression (PPD) and postpartum (puerperal) psychosis (PP)

- Not representative of the clinical reality
  - Potent and unique trigger of hypomania/mania
  - Childbirth triggers a variety of psychiatric disorders (e.g. OCD)
  - Baby blues is not a psychiatric disorder
  - Prepartum onset is common
  - Lacks specificity-no treatment guidance

Brockington I. The Lancet 2004; 363(9405):303-0.
DSM-5 Classification

- Peripartum onset specifier
  - For a manic, hypomanic or a major depressive episode (MDE) in the context of BD-I, BD-II, or MDD if episode onset is during pregnancy or 4 weeks postpartum
- Other psychiatric disorders
- First onset versus Recurrence
- Pregnancy onset versus Postpartum onset
- Short duration of the postpartum period

American Psychiatric Association. (2013). Diagnostic and Statistical Manual of Mental Disorders (5th ed.).
Duration of the Postpartum Period?

- DSM-5
  - 4 weeks following delivery
- WHO’s ICD-11 - “episodes that are associated with the puerperium” are required to onset of the episode within 6 weeks of delivery
- Range 3-12 months

American Psychiatric Association (2013)
Diagnostic and Statistical Manual of Mental Disorders (Fifth edition ed.)
Admissions to a Psychiatric Hospital: 2 Years Pre- and Post-Delivery

## Diagnosis Specific Risks of First-time Hospital Admissions 0-1 Month Postpartum Among First-time Mothers

<table>
<thead>
<tr>
<th>Diagnoses</th>
<th>Time since birth of first live-born child</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pregnancy</td>
<td>0-30 days</td>
</tr>
<tr>
<td>Schizophrenia; schizophrenia like and schizotypal disorders</td>
<td>18</td>
<td>32</td>
</tr>
<tr>
<td>No. of Cases</td>
<td>0.33 (0.19-0.59)</td>
<td>5.65 (3.47-9.20)</td>
</tr>
<tr>
<td>RR (95% CI)</td>
<td>0.19 (0.04-0.86)</td>
<td>23.33 (11.52-47.24)</td>
</tr>
<tr>
<td>Bipolar disorder</td>
<td>2</td>
<td>26</td>
</tr>
<tr>
<td>No. of Cases</td>
<td>0.44 (0.31-0.62)</td>
<td>2.79 (1.90-4.11)</td>
</tr>
</tbody>
</table>

Postpartum Psychosis

- Follows 1 in 500-1000 deliveries
- Onset usually within first 2 weeks after delivery—“an odd affect, withdrawn, distracted by auditory hallucinations, incompetent, confused, catatonic; or alternatively, elated, labile, rambling in speech, agitated or excessively active.”
- BD and a first-degree relative with PP--------74%
- BD without any family history of PP--------30%
- Risk of self harm and harm to infant
- A medical emergency (hospitalization is usually required)

Features of Postpartum Psychosis

- Latent class analysis (130 cases of PP) --**depressive** (41%), **manic** (34%) and **atypical** (disturbance of consciousness and disorientation) (25%)
- Most common symptoms of PP--irritability (73%), abnormal thought content (72%), and anxiety (71%)
- Suicidal and infanticidal ideation was present in 19% and 8% of patients, respectively
- **Common symptoms of depressive PP:** depression and anxiety, treatment was started 2 weeks later (P=.049), and more often voluntarily, than in manic and atypical women (P=.037)

Kamperman et al. Bipolar Disord 2017;Epub.
Early Postpartum Symptoms in Puerperal Psychosis (N=127)

The most commonly recalled symptoms were:
- feeling excited, elated or high (52%),
- not needing to sleep or not able to sleep (48%),
- feeling active or energetic (37%) and;
- talking more or feeling very chatty (31%)

Heron et al. BJOG 2008;115: 348–53.
Maternal Filicide and BD

- 45 women hospitalized after committing/ attempting filicide in Korea whose discharge diagnoses were MDD or BD
  - At admission, 24.4% of the patients had a diagnosis of BD; at discharge 73.3% of women had BD
  - 64.7% of women with MDD were subsequently reclassified as having BD
- The significant (p < .05) depressive symptoms at the time of filicide that could predict bipolar depression were:
  - Presence of postpartum-onset depression (95% CI = 1.45 to 160.88),
  - **Psychotic symptoms** (95% CI = 1.94 to 215.81), and
  - Non altruistic motivation for filicide (95% CI = 1.68 to 133.36)

Misdiagnosis of Bipolar PPD

- 56 women seen consecutively with the referral diagnosis of PPD (3 months) reassessed using the Structured Clinical Interview for DSM (SCID)
- SCID diagnosis MDD -46%, BD-54%
  - BD-NOS 29%
  - BD-II 23%
  - BD-I 2%

Over 80% of patients who scored positive on either the Highs Scale or the Mood Disorder Questionnaire (MDQ) met the diagnostic criteria for BD

Current comorbidity 32%
Anxiety disorder 46% (with 2/3 of women having OCD)
Bipolar II Disorder and PPD

- Retrospectively evaluated women with BD-I (93), BD-II (36) and MDD (444) for history of PPD
- 24% (139/573) had PPD
  - BD-II 50%
  - BD-I 27.5%
  - MDD 21.6%
- Women with a history of PPD were:
  - Younger
  - Younger at illness onset
  - Had more family history for BD

Ten thousand mothers of at least 18 years of age were screened 4-6 weeks postpartum by telephone.

Screen-positive women were invited to undergo psychiatric evaluations using the SCID in their homes:

- 14% had a positive screen (10 or more on Edinburgh Postnatal Depression Scale [EPDS])
- Episode onset---40% postpartum, 33% during pregnancy, and 27% before pregnancy
- 66% women were comorbid for an anxiety disorder

Wisner et al., JAMA Psych 2013; 70: 490-8.
Postpartum Depression and BD (contd.)

• 22.6% BD (26.7% in women with EPDS ≥ 13)
  • BD- I – 50%
  • BD- II – 31%
  • BD NOS – 19%

• Higher proportion of BD at a cut off of 13 or higher (26.7%)

• Secondary diagnoses in women with BD
  • Anxiety disorders 85%
  • Substance use disorder 12%
  • Eating disorders 3%
Bipolar PPD Manifest and Occult

• Depression occurring in the context of BD (type I, II, and other specified)
• Diagnostic switching from MDD to BD-II – 6.5% during the first 6 months postpartum (at least 11- to 18-fold higher than the rates of switching in similar studies conducted in both men and women)
• BD misdiagnosed as MDD
• Undeclared bipolarity e.g. in women with first onset of depression in the postpartum period (5.85%)
  • Depending on the criteria used, 15-50% develop BD

Thomson M, Sharma V. CNS Spectr 2017;22(S1):49-64.
American Psychiatric Association (2013). Diagnostic and statistical manual of mental disorders (5th ed.)
Consequences of Misdiagnosis of Bipolar PPD

- Bipolar PPD is common but often underdiagnosed or misdiagnosed
  - Lack of awareness
  - Lack of screening
  - Difficult to differentiate between joy and postpartum hypomania

- Consequences
  - Inappropriate treatment (injudicious use of ADs)
    - Risk of destabilization of mood at a critical time for the mother and her family
  - ↑ Psychiatric hospitalization
  - Reduced ability to care for the baby

Diagnostic Switching

- Women with MDD (92) or BD-II (54) recruited between 24 and 28 weeks' gestation and followed through to one year postpartum
- SCID at study intake and MINI at 1, 3, 6, and 12 months after childbirth
- Six women (6.52%) experienced a change from MDD to BD-II during the first 6 months postpartum
- No cases of switching from MDD to BD-I but in one participant the diagnosis changed from BD-II to BD-I during the 3 months
- Bipolar switch was associated with a family history of BD
Conversion Rates to Diagnoses of BD During a 15-year Follow-up Period

- 1-30 d Postpartum: 13.87% (95% CI = 10.00-17.58)
- 31-365 d Postpartum: 4.69% (95% CI = 3.47-5.90)
- Other points: 4.04% (95% CI = 3.85-4.21)
# Features Suggestive of Bipolarity in Women with PPD

<table>
<thead>
<tr>
<th>Illness onset</th>
<th>Younger age at illness onset</th>
</tr>
</thead>
<tbody>
<tr>
<td>First onset of depression during the postpartum period</td>
<td></td>
</tr>
<tr>
<td>Depression onset immediately after delivery</td>
<td></td>
</tr>
<tr>
<td>Illness course &amp; symptoms</td>
<td>High number of prior episodes</td>
</tr>
<tr>
<td>Brief episodes of depression</td>
<td></td>
</tr>
<tr>
<td>Depressive episodes with free intervals</td>
<td></td>
</tr>
<tr>
<td>Seasonality of mood episodes</td>
<td></td>
</tr>
<tr>
<td>Atypical features: hypersomnia, leaden paralysis or increased appetite</td>
<td></td>
</tr>
<tr>
<td>Mixed depression</td>
<td></td>
</tr>
<tr>
<td>Psychotic symptoms</td>
<td></td>
</tr>
<tr>
<td>History of bipolar disorder in a first degree relative</td>
<td></td>
</tr>
<tr>
<td>Treatment response</td>
<td>Atypical antidepressant response: <em>induction of mania, hypomania or mixed depressive episodes</em>; poor response; rapid response; loss of antidepressant response</td>
</tr>
</tbody>
</table>

# Postpartum Hypomania

<table>
<thead>
<tr>
<th>Study</th>
<th>Day 3 PP</th>
<th>6 Weeks PP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glover et al. 1994*</td>
<td>10.0%</td>
<td>7%</td>
</tr>
<tr>
<td>Lane et al. 1997</td>
<td>18.3%</td>
<td>9%</td>
</tr>
<tr>
<td>Hasegawa, M. 2000</td>
<td>13.5%</td>
<td>NA</td>
</tr>
<tr>
<td>Webster et al. 2003</td>
<td>9.6%</td>
<td>NA</td>
</tr>
<tr>
<td>Farías et al. 2007</td>
<td>20.4%</td>
<td>NA</td>
</tr>
<tr>
<td>Heron et al. 2009**</td>
<td>11.7%</td>
<td>4.9% (8 weeks)</td>
</tr>
</tbody>
</table>

* 11% had a score of > 8 on the Highs scale on Day 5 postpartum
** 1.4% of cases had hypomanic symptoms at 12 weeks of pregnancy

Postpartum Hypomania: A Canadian Study

• Prospective study
  • SCID administered to women with MDD at 4 times - ~26 weeks gestation, and 1 week, 4 weeks and 12 weeks postpartum
  • Using Altman Self-Rating Mania Scale the authors found 34.6% hypomania/mania (a score of ≥6) at ≥ 1 period PP
  • 24.6% at one week
  • For the majority of women (54%) the onset was postpartum, 4.7% scored above cut-off during pregnancy only

BD and Postpartum Morbidity

- Depression is the most common form of morbidity
- Most mood episodes occur in the first month postpartum
- Hypomania, mania and psychosis have an earlier onset than depression
- Higher risk of recurrences for BD-I than for BD-II

Di Florio et al., JAMA Psych 2013; 70: 168-75.
Risk Factors

Postpartum Mood Episodes

- Younger age
- Primiparity
- Unplanned pregnancy
- Prior postpartum episode (especially after first delivery)
- Family history of BD
- A diagnosis of BD-II
- Lack of maintenance pharmacotherapy pre-or post delivery
- Antenatal symptoms

Screening and Diagnosis
Screening for Depression in Primary Care

Systematic Review and Evidence Report for the US Preventive Services Task Force

• 18%-59% relative reduction, 2.1% to 9.1% absolute reductions in the risk of depression at follow-up (3-5 months) following participation in screening programs during pregnancy or postpartum + treatment compared with usual care

• The American College of Obstetricians and Gynecologists (ACOG) recommends: women should be screened for depression and anxiety symptoms at least once during the perinatal period

## PPD Screening Questionnaires

<table>
<thead>
<tr>
<th>Scale</th>
<th>Items</th>
<th>Time (Days)</th>
<th>Scoring</th>
<th>Positive Screen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Edinburgh Postnatal Depression Scale (EPDS)</td>
<td>10</td>
<td>7</td>
<td>30</td>
<td>&gt;10</td>
</tr>
<tr>
<td>Postpartum Depression Screening Scale</td>
<td>35</td>
<td>14</td>
<td>175</td>
<td>Cutoff score of 80 for major PPD Cutoff score of 60 for minor or major PPD</td>
</tr>
<tr>
<td>Patient Health Questionnaire-2 (PHQ-2)</td>
<td>2</td>
<td>14</td>
<td></td>
<td>May be answered in a “yes/no” format or via a (0- to 3-point Likert scale, for a total of 6</td>
</tr>
<tr>
<td>1. “Have you been bothered by little interest or pleasure in doing things?”</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. “Have you been bothered by feeling down, depressed or hopeless?”</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

An answer of “yes” to either question warrants a third question: “Is this something you feel you need help with?”

Screening for BD

- Universal screening during pregnancy
- Postpartum period
  - First-onset of depression in the postpartum period
  - Early psychiatric contact (4 weeks)
  - Psychotic depression
  - MDD with mixed features
  - History of postpartum hypomania
  - Family history of BD in a first-degree relative

Mood Disorder Questionnaire

Diagnosis of hypomania is positive if 7 or more items are endorsed in question 1, YES is the answer for question 2, and MODERATE or SERIOUS problem is checked for question 3. Sensitivity and specificity of these criteria compared with semi structured interviews are 73% and 90%, respectively.*

<table>
<thead>
<tr>
<th>INSTRUCTIONS: Please answer each question as best you can.</th>
<th>YES</th>
<th>NO</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Has there ever been a period of time when you were not your usual self and...</td>
<td></td>
<td></td>
</tr>
<tr>
<td>... you felt so good or so hyper that other people thought you were not your normal self or you were so hyper that you got into trouble?</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>... you were so irritable that you shouted at people or started fights or arguments?</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>... you felt much more self-confident than usual?</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>... you got much less sleep than usual and found that you didn't really miss it?</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>... you were more talkative or spoke much faster than usual?</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>... thoughts raced through your head or you couldn't slow your mind down?</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>... you were so easily distracted by things around you that you had trouble concentrating or staying on track?</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>... you had much more energy than usual?</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>... you were much more active or did many more things than usual?</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>... you were much more social or outgoing than usual, for example, you telephoned friends in the middle of the night?</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>... you were much more interested in sex than usual?</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>... you did things that were unusual for you or that other people might have thought were excessive, foolish or risky?</td>
<td>○</td>
<td>○</td>
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<tr>
<td>... spending money got you or your family in trouble?</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>2. If you checked YES to more than one of the above, have several of these ever happened during the same period of time?</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>3. How much of a problem did any of these cause you - like being able to work; having family, money or legal troubles; getting into arguments or fights?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>O No problem</td>
<td>O Minor problem</td>
<td>O Moderate problem</td>
</tr>
<tr>
<td>4. Have any of your blood relatives (i.e. children, siblings, parents, grandparents, aunts, uncles) had manic-depressive illness or bipolar disorder?</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>5. Has a health professional ever told you that you have manic-depressive illness or bipolar disorder?</td>
<td>○</td>
<td>○</td>
</tr>
</tbody>
</table>

Peripartum Screening for BD: Mood Disorders Questionnaire

Alternate scoring:
sensitivity of 87.72% [95% CI: 76.32%–94.92%] and
specificity of 85.29% [95%CI: 74.61%–92.72%]

Traditional scoring:
sensitivity of 75.44% [95%CI: 62.24%–85.87%] and a
specificity of 86.76% [95%CI: 76.36%–93.77%]

# Use of Mood Diary

## Record Hours of Nighttime Sleep

<table>
<thead>
<tr>
<th>Date</th>
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<tbody>
<tr>
<td>1</td>
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<td>30</td>
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<tr>
<td>31</td>
</tr>
</tbody>
</table>

## Dystrophic Mania

- **Severe**: Essentially incapacitated or hospitalized
- **High Moderate**: Great difficulty with goal-oriented activity
- **Low Moderate**: Some difficulty with goal-oriented activity
- **Mild**: More energized & productive with little or no functional impairment

## Stable

- **Mild**: Little or no functional impairment
- **Low Moderate**: Functioning with some effort
- **High Moderate**: Functioning with great effort
- **Severe**: Essentially incapacitated or hospitalized

## Mood (0-100)

- **Mood**: Most depressed ever, Balanced, Most manic (activated) ever

<table>
<thead>
<tr>
<th>Mood Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
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<tr>
<td>50</td>
</tr>
<tr>
<td>50</td>
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<tr>
<td>70</td>
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<td>50</td>
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<tr>
<td>45</td>
</tr>
<tr>
<td>60</td>
</tr>
</tbody>
</table>

## Number of Mood Switches per Day

- **Number of Mood Switches**: 1 per day

## Menstrual Period

- **Menstrual Period**: Yes

## Table

| Week | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25 | 26 | 27 | 28 | 29 | 30 | 31 |
|------|---|---|---|---|---|---|---|---|---|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|
Screening Algorithm

Screen with EPDS

Positive Screen

Screen with MDQ

Positive Screen

Assess to determine diagnosis

BPD

BPD 1

BPD 2

Other Specified Bipolar & Related Disorder

Negative Screen

Assess to determine diagnosis

MDD with Mixed Features

MDD without Mixed Features

Abbreviations:
BPD = Bipolar Disorder
EPDS = Edinburgh Postnatal Depression Scale
MDD = Major Depressive Disorder
MDQ = Mood Disorder Questionnaire

Thomson M, Sharma V. CNS Spectr 2017;22(S1):49-64.
Screening Comorbidities

- “Do you have unpleasant thoughts, urges or images that repeatedly enter your mind?”

- “Do you feel driven to perform certain behaviours or mental acts over and over again?”

- Yale Brown Obsessive Compulsive Scale (Y-BOCS)

- Generalized Anxiety 7-item (GAD-7) scale
Assessment for PPD

- Comprehensive diagnostic assessment (symptoms and syndromes)
  - MDE versus antidepressant withdrawal
  - First onset versus recurrence
  - Timing of onset (pregnancy versus postpartum)
  - Illness course (history of peripartum episodes)
  - Symptom severity and safety issues
  - Sleep (< 8 hours had higher risk of depression and anxiety)
- Treatment history and response

Familiality of Postpartum Psychiatric Disorders

• ↑ relative risk of psychiatric disorders in first time mothers when first degree family members had a psychiatric disorder (hazard ratio=1.45, 95% CI=1.28-1.65)

• Highest risk when there was a history of BD in a first-degree family member (hazard ratio=2.86, 95% CI=1.88-4.35)

• Obtaining family history of psychiatric illness especially BD should assist in the identification of women at risk for postpartum psychiatric disorders

Differential Diagnosis

- Baby blues
  - 50-85% of women within first 2 weeks after delivery, mood lability, tearfulness, sleep disturbance, and no treatment is needed
- Bereavement
- MDD with mixed features
- Postpartum thyroiditis (TSH, free T4 and thyroid peroxidase)

Postpartum Management

• Women stable on a mood stabilizer (MS) or an atypical antipsychotic (AAP) should continue with the same after delivery

• For medication-free women, consider trial of a previously effective MS or an AAP (lack of effectiveness of valproate) OR follow the algorithm for non-postpartum mood episodes

• Compatibility of medications with breastfeeding

Postpartum Management

• Location of treatment and status
  • Postpartum psychosis is a psychiatric emergency; Inpatient psychiatric treatment is essential to ensure the safety of mother and baby

• Physical examination and investigations including CBC, complete blood chemistry, thyroid function and antithyroid antibody tests, and calcium, vitamin B\textsubscript{12}, and folate levels

• Acute, maintenance and prophylactic treatment

Acute Treatment of Bipolar PPD

• A chart review of 18 women treated with quetiapine alone or in combination with hypnotics
  • Median: 75 mg
  • Range: 12.5 - 500 mg
• 83% were very much or much improved on retrospective Clinical Global Impression Scale
• A chart review of 26 women treated with quetiapine XR
  • Only 12 of 26 women who were enrolled in the 12-week open trial completed the study; 87% asymptomatic by week 14
  • Mean dose: 137.5 mg

# RCTs of ADs in PPD

<table>
<thead>
<tr>
<th>Authors (year)</th>
<th>Study Design</th>
<th>N</th>
<th>Length (weeks)</th>
<th>Groups</th>
<th>Response Rate (% int{a} vs % CNT)</th>
<th>Remission Rate (% int{a} vs CNT)</th>
<th>Antidepressant Dose (mg/day)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hantsoo et al. (2014)</td>
<td>DB-RPCT{a}</td>
<td>38</td>
<td>6</td>
<td>SER{a} vs PBO{a}</td>
<td>59 vs 26 (p = 0.05)</td>
<td>53 vs 21 (p = 0.05)</td>
<td>SER: 50 – 200 Mean dose 100 SER and 119.4 PBO</td>
<td>Benefits of SER more pronounced when MDD{e} onset within 4 weeks</td>
</tr>
<tr>
<td>Bloch et al. (2012)</td>
<td>DB-RPCT</td>
<td>44</td>
<td>8</td>
<td>SER + BPD{e} vs PBO + BPD</td>
<td>70 vs 55 (p = 0.33)</td>
<td>65 vs 50 (p = 0.34)</td>
<td>SER: 50 – 100 Mean dose 87.5 SER and 62.5 PBO</td>
<td>SER did not add significant benefit vs PBO when added to BPD</td>
</tr>
<tr>
<td>Sharp et al. (2010)</td>
<td>RCT{b}</td>
<td>254</td>
<td>18</td>
<td>ADs{d} vs supportive counselling</td>
<td>45 vs 20 at 4 weeks (p &lt; 0.001)</td>
<td>62 vs 51 at 18 weeks (p = 0.19)</td>
<td>N/A</td>
<td>Not reported</td>
</tr>
<tr>
<td>Yonkers et al. (2008)</td>
<td>DB-RCT</td>
<td>70</td>
<td>8</td>
<td>PAR{e} vs PBO</td>
<td>43 vs 31 (p = 0.94)</td>
<td>37 vs 15 (p = 0.04)</td>
<td>PAR: 10-50 Mean dose 21.1 ± 10.7 PAR</td>
<td>No significant improvements in CGI-S{m} (p=0.05), HDRS{b} or IDS-SR{a}</td>
</tr>
<tr>
<td>Wisner et al. (2008)</td>
<td>RCT</td>
<td>109</td>
<td>8 initial, 16 follow up</td>
<td>SER vs NOR{f}</td>
<td>80 vs 77 at 8 weeks (p = 1.0)</td>
<td>93 vs 100 at 20-24 weeks (p = 1.0)</td>
<td>67 vs 55 at 8 weeks (p=1.0)</td>
<td>No differences in response and remission between SER and NOR at 4, 8 and 24 weeks</td>
</tr>
<tr>
<td>Misri et al. (2004)</td>
<td>RCT</td>
<td>35</td>
<td>12</td>
<td>PAR vs PAR + CBT{i}</td>
<td>87.5 vs 78.9 (p = 0.60)</td>
<td>N/A</td>
<td>PAR: 10-50 Mean dose in monotherapy group was 36.25 Mean dose in PAR + CBT group was 32.50</td>
<td>Both PAR monotherapy and PAR with CBT were efficacious in improving mood and anxiety but no additional benefit of adding CBT</td>
</tr>
<tr>
<td>Appleby et al. (1997)</td>
<td>DB-RCT</td>
<td>87</td>
<td>12</td>
<td>FLU vs PBO. Both had 1 or 6 counselling sessions</td>
<td>N/A</td>
<td>N/A</td>
<td>20</td>
<td>Additional benefit seen from 6 vs 1 sessions of counselling or adding FLU but no advantage to adding both</td>
</tr>
</tbody>
</table>

**Abbreviations:**

{a}DB-RCT: double-blind randomized placebo controlled trial, {b}RCT: randomized controlled trial (non-placebo), {c}SER: sertraline, {d}PBO: placebo, {e}BPD: Brief psychodynamic therapy, {f}ADs: antidepressant medications, {g}PAR: paroxetine, {h}NOR: nortriptyline, {i}CBT: cognitive behavioural therapy, {j}FLU: fluoxetine, {k}int: intervention group, {m}MDD: major depressive disorder, {m}CGI-S: Clinical Global Improvement Scale – Severity, {n}HDRS: Hamilton Depression Rating Scale, {o}ISD-SR: Inventory of Depressive Symptomatology-Self Report

# Preventative Effect of ADs in PPD

Summary of antidepressant trials in the prevention of postpartum depression

<table>
<thead>
<tr>
<th>Authors (year)</th>
<th>Study design</th>
<th>Sample size</th>
<th>Duration (in weeks)</th>
<th>Intervention</th>
<th>Recurrence rate (%)</th>
<th>Antidepressant dose (daily)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wisner and Wheeler (1994)</td>
<td>Open trial</td>
<td>23</td>
<td>12</td>
<td>Postpartum monitoring vs. postpartum monitoring plus ADs</td>
<td>62.5 6.7</td>
<td>Known effective dose of a previously tried AD or NOR</td>
</tr>
<tr>
<td>Wisner et al. (2001)</td>
<td>DB-RCT</td>
<td>55</td>
<td>20</td>
<td>NOR vs. PBO</td>
<td>23 24</td>
<td>Dose gradually increased from 10 to 75 mg</td>
</tr>
<tr>
<td>Wisner et al. (2004)</td>
<td>DB-RCT</td>
<td>22</td>
<td>17</td>
<td>SER vs. PBO</td>
<td>7 50</td>
<td>Dose gradually increased from 25 to 75 mg</td>
</tr>
<tr>
<td>Yonkers et al. (2011)</td>
<td>Prospective cohort</td>
<td>778</td>
<td>12</td>
<td>112 women took one type of antidepressant, 16 took two types and 2 took three types</td>
<td>The hazard ratio for ADs users compared with non-users was 0.88 (95% CI = 0.51 - 1.5)</td>
<td>Doses consistent with the manufacturers’ recommended actions</td>
</tr>
</tbody>
</table>

AD antidepressant, DB-RCT double-blind, randomized controlled trial, NOR nortriptyline, PBO placebo, SER sertraline

Antidepressants and Postpartum Depression

- Rule out BD
- Taper off AD if the patient develops postpartum psychosis/mania

AVOID or use with CAUTION

- MDD with mixed features
- AD-naive women
- MDE with first onset in the postpartum period
- MDE with onset in early postpartum period
- History of BD in a first degree relative
- Atypical features: hypersomnia, leaden paralysis, or increased appetite

# Strategies for Prevention or Early intervention in Women at Risk of Developing BD

<table>
<thead>
<tr>
<th>Clinical Presentation</th>
<th>Therapeutic Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>No current or past psychiatric disorder</td>
<td>• Close monitoring&lt;br&gt;• Optimize sleep&lt;br&gt;• Ensure social support&lt;br&gt;• Lifestyle management, physical activity, diet, smoking cessation</td>
</tr>
<tr>
<td>Subthreshold hypomanic, or manic symptoms</td>
<td>• Optimize sleep&lt;br&gt;• Consider low dose BZD or atypical neuroleptics especially in primigravida women</td>
</tr>
</tbody>
</table>
## Strategies for Prevention or Early intervention in Women at Risk of Developing BD

<table>
<thead>
<tr>
<th>Clinical Presentation</th>
<th>Therapeutic Options</th>
</tr>
</thead>
</table>
| Psychiatric disorders that commonly accompany BD such as AD, Obsessive-compulsive disorder (OCD) or SUD | • Psychotherapy  
• Ensure access to prevention and treatment services for SUD  
• Low dose BZD or atypical neuroleptics  
• Antidepressant monotherapy is not recommended |
| Current MDE | • Psychotherapy for MDE of mild to moderate severity  
• Quetiapine §, lamotrigine or lurasidone for severe MDE and high risk of switching  
• Severe MDE and low risk of switching a cautious trial of the same or another AD with a low risk of manic switch |

Sharma et al. Lancet Psychiatry, 2019 6(9): 786-792.
Neonatal Discontinuation Syndrome
Antidepressant versus Mood Disorder exposure

- Secondary analysis of 2 observational studies in Cleveland and Pittsburgh
  - Serotonin reuptake inhibitor (SRI)-exposed group, mood disorder group, and comparison group
  - Rates (defined as a score of ≥ 2 on the Finnegan Scale) were 34.1%, 35.1%, and 30.4% respectively
  - Higher rate of preterm birth (24.4%) in the SRI exposed group compared to the other groups (7.4% and 8.9%)
  - Preterm births had a significantly higher sign rate compared to full-term newborns (54% versus 31%, \( p = .020 \))
  - Neonatal signs at 2-4 weeks were more closely associated with prematurity than with utero SRI or MD exposure

Psychological Interventions

- Pharmacotherapy is the foundation for treatment
- Adjunctive psychosocial interventions may be useful for acute depressive episodes
- There are no 1st-line psychosocial treatment options
- Selecting between 2nd-line (CBT, IPSRT) and 3rd-line options should be based on individual strengths and needs
Prognosis

• Compared to non-postpartum onset, the postpartum-onset is associated with:
  • Fewer recurrences of manic/mixed episodes but not of depression
  • ? different trajectories or treatment response for pregnancy onset versus postpartum onset
  • ? whether episodes with first onset after childbirth tend to occur only in the postpartum period

Prevention and Treatment

- Identify at-risk women, regular follow-up, discuss strategies for adequate sleep (history of mania following sleep loss could be a marker of increased vulnerability to PP)
- Early identification (pre-partum) and symptom management/prophylactic use of medication
- Lithium is the most studied drug
- Relapse risk of PP/mania among medicated (23%) versus unmedicated 66%
- Antipsychotic medications, benzodiazepines, ECT are useful adjuncts
- Avoid ADs even in women with depressive psychosis!

Lithium and Lactation

- Quantified lithium exposure in nursing infants (10 mother-infant pairs)
- Maternal serum, breast milk, and infant serum daily trough concentrations of lithium averaged 0.76, 0.35, and 0.16 meq/liter, respectively (RULE of HALVES)
- Hydrophilic drugs (↑ hind milk)--- hydrophilic lithium showed no such concentration gradient

**Suitable clinical characteristics:**
- Stable maternal mood
- Lithium monotherapy
- Adherence to infant monitoring
- A healthy infant and a collaborative pediatrician

Other Mood Stabilizers and Lactation

- Considerable amount of LTG is excreted into breast milk
- Paucity of data on valproate; however, the infant/maternal ratio of serum drug concentration seems to be lower in valproate exposure compared to other MS
- Incidence of adverse events in infants exposed to MS is reported to be very low
- MS can be prescribed without any adverse events in most infants in lactating women
- Low prevalence rate of lab abnormalities including hepatic, kidney, and thyroid functions in the infants

## Psychiatric Medications and Lactation

<table>
<thead>
<tr>
<th>Agent</th>
<th>Lactation risk category**</th>
<th>Agent</th>
<th>Lactation risk category**</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anxiolytic medications</strong></td>
<td></td>
<td><strong>Nonbenzodiazepine anxiolytics and hypnotics</strong></td>
<td></td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td></td>
<td>Antipsychotic medications</td>
<td></td>
</tr>
<tr>
<td>Alprazolam</td>
<td>L3</td>
<td>Buspirone</td>
<td>L3</td>
</tr>
<tr>
<td>Chlordiazepoxide</td>
<td>L3</td>
<td>Chlroral hydrate</td>
<td>L3</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>L3</td>
<td>Eszopiclone</td>
<td>N/A</td>
</tr>
<tr>
<td>Clorazepate</td>
<td>L3</td>
<td>Zaleplon</td>
<td>L2</td>
</tr>
<tr>
<td>Diazepam</td>
<td>L3, L4 if used chronically</td>
<td>Zolpidem</td>
<td>L3</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>L3</td>
<td>Antiepileptic and mood stabilizing medications</td>
<td>Perphenazine</td>
</tr>
<tr>
<td>Oxazepam</td>
<td>L3</td>
<td>Lithium carbonate</td>
<td>L4</td>
</tr>
<tr>
<td><strong>Benzodiazepines for insomnia</strong></td>
<td></td>
<td>Valproic acid</td>
<td>L2</td>
</tr>
<tr>
<td>Estazolam</td>
<td>L3</td>
<td>Carbamazepine</td>
<td>L2</td>
</tr>
<tr>
<td>Flurazepam</td>
<td>L3</td>
<td>Lamotrigine</td>
<td>L3</td>
</tr>
<tr>
<td>Quazepam</td>
<td>L2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Temazepam</td>
<td>L3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triazolam</td>
<td>L3</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Lactation risk categories are listed as follows:**
- L1 = safest;
- L2 = safer;
- L3 = moderately safe;
- L4 = possibly hazardous;
- L5 = contraindicated.

As of 2015, the US Food and Drug Administration (FDA) discontinued the pregnancy risk categories (ABCDX)

The ABCDX system has been replaced by the FDA Pregnancy and Lactation Labeling Rule (PLLR) that requires narrative text to describe risk information, clinical considerations, and background data for the drug

The new rule includes 3 overarching categories: 1) pregnancy, which includes labour and birth; 2) lactation; and 3) females and males of reproductive potential
FDA Pregnancy and Lactation Labeling Final Rule

Prescription Drug Labeling Sections 8.1 - 8.3 USE IN SPECIFIC POPULATIONS

CURRENT LABELING

8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers

NEW LABELING (effective June 30, 2015)

8.1 Pregnancy includes Labor and Delivery
8.2 Lactation includes Nursing Mothers
8.3 Females and Males of Reproductive Potential

U.S. Food and Drug Administration
https://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/labeling/ucm093307.htm
Childbirth: an Unparalleled Opportunity

- Potential contributions of perinatal research to the field of mental health have yet to be realized
  - Hormonal changes, sleep loss, substance use, ADs
  - Relationship between COMORBID disorders
- Primary prevention and early intervention
  - Women are routinely under the care of health professionals
  - Targeting putative risk factors—or sleep loss, substance use, and use of antidepressants
  - Short duration of the risk period for occurrence of postpartum mood episodes—especially hypomania or mania
- Transmission of psychopathology across generations

Sharma et al. Lancet Psychiatry 2019; 6(9): 786-792.
Postpartum-onset OCD and BD

### Mania

- **Severe**: 3
- **Moderate**: 2
- **Mild**: 1
- **Mild**: -1
- **Moderate**: -2
- **Severe**: -3

### Depression

- **Mild**: 1
- **Moderate**: 2
- **Severe**: 3

#### 2010
- Anxiety (premenstrual worsening)
- Treated with BZDs

#### 2011
- **Postpartum OCD (1st child)**
  - SER 50mg

#### 2012
- Depressive episode with suicide attempt

#### 2013
- **Pregnancy**
  - SER 150mg
- **Postpartum**
  - SER 150mg and ARI 2mg

#### 2016
- Mixed episode with hospitalization.

**Current Medications**
- LI 750mg daily
- QUE 500mg daily
- RIS 0.5mg daily
Is bipolar postpartum depression overlooked?

Q and A
Case Vignettes
Case #1 – Luna

What is your immediate course of action?
Case #1 – Luna

What is your immediate course of action?

- Find out whether Luna has been using birth control (she then tells you she has been taking oral contraceptives for the last 6 months)

- Tell her that with careful planning and close follow up, she should be able to start a family
Case #1 – Luna

What questions should you ask?
Case #1 – Luna

What questions should you ask?

• When are you planning on becoming pregnant?

• What medications are you taking? (to ensure current medications do not interfere with the efficacy of her birth control)

Case #1 – Luna

What is your treatment plan?
Case #1 – Luna

What is your treatment plan?

- Recommend that Luna meet with you again at least 3 months before she plans to become pregnant.
Case #1 – Luna

What is your treatment plan? (1 month pregnant)

Case #1 – Luna

What is your treatment plan? (1 month pregnant)

- Discuss the risk of not treating her depression versus risk of teratogenicity of medications
- Decide lamotrigine is best option (low risk of teratogenicity and adverse effects while breastfeeding)
- Caution Luna about risk factors for recurrence during the postpartum period and recommend her mother stay with her to ensure she does not become sleep deprived
Case #2 – Gabriella

What is your diagnosis?
Case #2 – Gabriella

What is your diagnosis?

- Major depressive disorder with mixed features

Is there a relationship between pre-eclampsia and first-onset postpartum psychiatric disorder?
Case #2 – Gabriella

What is your diagnosis?

• Major depressive disorder with mixed features

Is there a relationship between pre-eclampsia and first-onset postpartum psychiatric disorder?

• Yes
• Both are more common in first-time mothers
Case #2 – Gabriella

What is your treatment plan?
Case #2 – Gabriella

What is your treatment plan?

- A trial of olanzapine
- Later had carbamazepine added to it
Case #3 – Angelica

What is your treatment plan?
Case #3 – Angelica

What is your treatment plan?

- Close monitoring
- Optimize sleep
- Ensure social support
- Lifestyle management (physical activity, diet, smoking cessation)
Case #3 – Angelica

At 37 weeks’ gestation, she develops insomnia, irritability, and has racing thoughts.

What is your treatment plan?
Case #3 – Angelica

At 37 weeks’ gestation, she develops insomnia, irritability, and has racing thoughts.

What is your treatment plan?
• Quetiapine 12.5 mg at bedtime

Follow Up:
• Was able to breastfeed for 6 months
• Did not have a recurrence of PPD
• Has remained symptom free for 12 months
Case #4 – Sabrina

What is your diagnosis?
Case #4 – Sabrina

What is your diagnosis?

- Other specified and related disorder
- Hair pulling disorder
Case #4 – Sabrina

What is your treatment plan?
Case #4 – Sabrina

What is your treatment plan?

• Taper off the antidepressant
• Try lithium monotherapy
Case #4 – Sabrina
Case #5 – Isabella

What is your diagnosis?
Case #5 – Isabella

What is your diagnosis?

• Major depressive disorder but at high risk of conversion to bipolar disorder
Case #5 – Isabella

What is your treatment plan?
Case #5 – Isabella

What is your treatment plan?

• Taper off vortioxetine

• Start quetiapine 12.5 – 25 mg at bedtime

• Stay on escitalopram 10 mg daily
Case #6 – Anna

What is your diagnosis?
Case #6 – Anna

What is your diagnosis?

• Major depressive disorder
Case #6 – Anna

What is your treatment plan?
Case #6 – Anna

What is your treatment plan?

- Started on citalopram 20 mg daily
- Added risperidone
- Substituted citalopram with venlafaxine and then bupropion
- Risperidone discontinued and added quetiapine
Case #6 – Anna

How would you re-evaluate this patient?
Case #6 – Anna

How would you re-evaluate this patient?

• Diagnosed with MDD with psychotic features

• ? Bipolar disorder – mixed episode

• Bupropion was tapered off and treatment continued with quetiapine 325 mg daily

• Marked improvement in her condition and the patient was discharged home within a few weeks
Case #6 – Anna

Long-Term Outcome

• Continued to do well for 6 years after the birth of her third child
• Developed depression, family doctor prescribed citalopram
• Developed a manic episode with persistence of symptoms following the discontinuation of the AD
• Diagnosis changed to bipolar I disorder
• Currently being treated with lithium and quetiapine
Case #7 - Sophia

What is your treatment plan? (Postpartum OCD)
Case #7 - Sophia

What is your treatment plan? (Postpartum OCD)

• Started on sertraline 50 mg daily
Case #7 - Sophia

What is your treatment plan?  
(First onset of depression during pregnancy)
Case #7 - Sophia

What is your treatment plan?
(First onset of depression during pregnancy)

• Increased sertraline to 150 mg daily
Case #7 - Sophia

What is your treatment plan?
(Recurrence of depression postpartum)
Case #7 - Sophia

What is your treatment plan?
(Recurrence of depression postpartum)

• Continued sertraline 150 mg daily and added aripiprazole 2 mg daily
Case #7 – Sophia

**Mania**

- Severe
- Moderate
- Mild

**Depression**

- Mild
- Moderate
- Severe

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010</td>
<td>Pregnancy</td>
<td>SER 150mg</td>
</tr>
<tr>
<td>2012</td>
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<td>SER 50mg</td>
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<tr>
<td>2012</td>
<td>Postpartum</td>
<td>SER 150mg and ARI 2mg</td>
</tr>
<tr>
<td>2016</td>
<td>Mixed episode with hospitalization.</td>
<td></td>
</tr>
</tbody>
</table>

**Current Medications**

- LI 750mg daily
- QUE 500mg daily
- RIS 0.5mg daily

**Symptom Ratings**

- YMRS = 5

Anxiety (premenstrual worsening) Treated with BZDs

Postpartum OCD (1st child) SER 50mg

Postpartum SER 150mg and ARI 2mg

Mixed episode with hospitalization.
Thank You