To Treat or Not to Treat, That is the Question: The Prevention of Postpartum Psychosis

Pharmacotherapy Grand Rounds

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Learning Objectives:
1. Describe the diagnosis, risk factors, and consequences of postpartum psychosis
2. Explain potential prevention options, including risks and benefits
3. Evaluate the literature for evidence of effective treatments
4. Develop an evidence-based approach for the prevention of postpartum psychosis
I. **Diagnosis**\(^1-6\)
   a. Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) does not recognize PP as a separate disorder
      i. Included in general “mood disorders” category
      ii. Non-distinguishable from non-postpartum psychoses
      iii. Postpartum onset specifier: must be within 4 weeks of delivery
   b. Differential diagnosis for PP episodes can include major depression with psychotic features, bipolar I, bipolar II, schizoaffective, unspecified functional psychosis, and brief psychotic disorder
   c. Often confused with postpartum depression
      i. Postpartum depression
         1. Affects 13% of mothers within 12 weeks of giving birth
         2. Non-psychotic depression
         3. Often requires treatment
      ii. PP
         1. Rare, affecting one to two per 1,000 deliveries
         2. More severe, often requiring hospitalization
         3. Characterized by delusions, hallucinations, bizarre behavior, depression, mania, and mood lability that usually presents within the first 2 weeks postpartum
         4. Atypical characterization of mixed affective state, confusion, and disturbed behavior
         5. Early onset and rapid progression, therefore a psychiatric emergency requiring prompt recognition

II. **Risk factors**\(^2,7-9\)
   a. History of bipolar disorder (BPD)
      i. Sevenfold higher risk of admission for a first episode and a nearly twofold higher risk for a recurrent episode compared with nonpostpartum and nonpregnant women
      ii. 32 – 67% experience relapse of affective symptoms postpartum
      iii. 25 – 50% will experience an episode of PP
      iv. Highest risk of admission within the first 30 days of postpartum period compared to other psychiatric disorders, including schizophrenia
   b. Personal history of PP predisposes approximately 57% of women to experience another episode after a subsequent pregnancy
   c. Family history - rates as high as 74% have been reported with women who also have a family history of PP
   d. Discontinuation of mood stabilizer prophylaxis
   e. Delivery complications
   f. Primiparity
   g. Sleep loss following pregnancy
III. **Pathophysiology of PP**

a. Etiologic factors
   i. Genetic predisposition
   ii. Hormonal changes

b. Pathological theories

![Figure 1: Pathological Theories](image)

Figure 1: Pathological Theories

c. Complicating causes
   i. External aggravating causes
      1. Lack of support received from father and family
      2. Unplanned pregnancy
      3. Marital discord
   ii. Obsession with being a good mother becomes a delusion

IV. **Consequences of PP**

a. Impaired mother-infant bonding
b. Infant abuse and neglect
c. Effect on child’s cognitive and emotional development
d. Risk of recurrent psychiatric illness in the mother
e. Suicide
f. Infanticide

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**Considerations in Pregnancy**

I. **FDA pregnancy category**

a. No psychotropic drugs have been approved for use during pregnancy
b. For ethical reasons, not possible to conduct randomized, placebo-controlled studies
c. Most information is derived from case reports or retrospective studies

### Table 1: FDA Pregnancy Category

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Controlled studies show no risk, safe for use during pregnancy</td>
</tr>
<tr>
<td>B</td>
<td>No evidence of risk in humans</td>
</tr>
<tr>
<td>C</td>
<td>Risk cannot be ruled out, but benefit may outweigh risk</td>
</tr>
<tr>
<td>D</td>
<td>Positive evidence of risk, but benefit may outweigh risk</td>
</tr>
<tr>
<td>X</td>
<td>Contraindicated by demonstrating fetal risks that outweigh benefit</td>
</tr>
</tbody>
</table>
II. **Organogenesis and fetal abnormalities**

a. Basic formation of organs occurs early in pregnancy, nearly complete by 12 weeks
b. Pregnancy is often not confirmed until organogenesis has already occurred
c. Teratogens interfere with organogenesis and produce malformations
d. Organ systems are susceptible during various times throughout the first trimester

![Figure 2: Review of Organogenesis](image)

III. **Pharmacokinetic changes during pregnancy**

a. Absorption
   i. Reduced gastric emptying and small intestine motility due to progesterone
   ii. Nausea and vomiting
b. Distribution
   i. Increase in volume of distribution for hydrophilic drugs
   ii. Decreased protein binding due to hemodilution
c. Metabolism
   i. Induction or inhibition of cytochrome P450 by estrogen and progesterone
   ii. Biliary system may be attenuated due to cholestatic property of estrogen
d. Elimination
   i. Renal blood flow increases by 60-80%
   ii. Glomerular filtration rate rises by 50%

IV. **Therapeutic drug monitoring of lithium (Li) in pregnancy and postpartum women**

a. Li is renally eliminated without biotransformation
b. In pregnancy, renal clearance doubles, lowering serum concentrations and increasing risk of relapse
c. More frequent drug monitoring has been recommended during pregnancy
   i. Every 2-4 weeks during pregnancy
   ii. Weekly during last month
   iii. Established therapeutic drug level (0.6-1.2 mEq/L)
d. At delivery, vascular volume rapidly decreases by approximately 40% and renal Li clearance falls to pre-pregnancy levels, increasing risk of toxicity
e. Reduce dose to pre-pregnancy levels after delivery, checking levels 24 hours and every few days after delivery
Treatment Options for the Prevention of PP

I. Pharmacologic agents\textsuperscript{13,20}
   a. Effectiveness has been shown with some agents
   b. Timing is controversial given risks and benefits
   c. Mood stabilizers\textsuperscript{13,20-23}

Table 2: Fetal Risks Associated with Mood Stabilizers Used in Pregnancy

<table>
<thead>
<tr>
<th>Drug</th>
<th>Proposed Mechanism of Action</th>
<th>Risk in pregnancy</th>
<th>Pregnancy category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Li</td>
<td>Alters sodium transport in nerve and muscle cells and affects a shift toward intraneuronal metabolism of catecholamines</td>
<td>● Ebstein’s cardiac malformation&lt;br&gt;● Neonatal hypothyroidism, diabetes insipidus&lt;br&gt;● Cyanosis, hypotonicity&lt;br&gt;● Secreted in breast milk</td>
<td>D</td>
</tr>
<tr>
<td>Divalproex</td>
<td>Potentiate or mimic the effects of the inhibitory neurotransmitter, gamma-aminobutyric acid (GABA)</td>
<td>● Neural tube defects&lt;br&gt;● Structural defects of heart, limbs, dysmorphic facies&lt;br&gt;● Secreted in breast milk</td>
<td>D</td>
</tr>
<tr>
<td>Carbamazepine (CBZ)</td>
<td>Reducing polysynaptic responses and blocking the post-tetanic potentiation</td>
<td>● Neural tube defects&lt;br&gt;● Developmental delay&lt;br&gt;● Dysmorphic facies&lt;br&gt;● Secreted in breast milk</td>
<td>D</td>
</tr>
</tbody>
</table>

   d. Antipsychotics\textsuperscript{13,20,24}

Table 3: Fetal Risks Associated with Olanzapine Used in Pregnancy

<table>
<thead>
<tr>
<th>Drug</th>
<th>Proposed Mechanism of Action</th>
<th>Risk in pregnancy</th>
<th>Pregnancy category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olanzapine</td>
<td>Combination of DA and serotonin type 2 (5HT\textsubscript{2}) antagonism</td>
<td>● Unknown risk for toxicity&lt;br&gt;● Metabolic syndrome, gestational diabetes&lt;br&gt;● Secreted in breast milk</td>
<td>C</td>
</tr>
</tbody>
</table>

   e. Hormone therapy\textsuperscript{13,20,25}

Table 4: Fetal Risks Associated with Hormone Therapy Used in Pregnancy

<table>
<thead>
<tr>
<th>Drug</th>
<th>Proposed Mechanism of Action</th>
<th>Risk in pregnancy</th>
<th>Pregnancy category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estrogen</td>
<td>Sudden withdrawal of estrogen, may modulate DA and 5HT in limbic system</td>
<td>● Endometrial hyperplasia&lt;br&gt;● Thrombosis</td>
<td>X</td>
</tr>
<tr>
<td>Progesterone</td>
<td>Poorly documented, metabolites may have anxiolytic properties</td>
<td>● Depression</td>
<td>B</td>
</tr>
</tbody>
</table>

   f. Additional pharmacological agents (Appendix A)
II. **Psychosocial interventions**
   a. No controlled clinical trials have evaluated nonpharmacological interventions in prevention of psychosis in pregnancy
      i. Discuss issue of pregnancy and management with every patient with BPD
      ii. Minimize sleep deprivation
      iii. Structured daily activity

III. **Treating potentially child-bearing women with mental illness**
   a. Risks associated with and without treatment that have not been fully quantified
      i. Exchange risk of medication exposure with risk of untreated mental illness
      ii. Impact of psychiatric illness on pregnancy outcome
         1. Increased incidence of low birth weight
         2. Decreased fetal growth
         3. Postnatal complications
         4. Poor compliance with prenatal care
         5. Inadequate nutrition
         6. Increased alcohol and tobacco use
   b. Planning for pregnancy while patient is euthymic
      i. Pregnancy tests
      ii. Thoughtful treatment choices
      iii. Avoid changing treatment during pregnancy
   c. Decision regarding continuing or initiating treatment during pregnancy must reflect an assessment of the following:
      i. Risk of fetal exposure to drugs
      ii. Risks to patient, fetus, and family of untreated mental illness
      iii. High risk of relapse associated with discontinuation of treatment
   d. General principles in managing BPD during pregnancy
      i. Planned pregnancy provides time for thoughtful treatment options
      ii. Streamline regimen
      iii. Use minimum effective dose
      iv. Consider a patient a “high-risk” pregnancy and monitor closely
      v. Consider pregnancy and postpartum period separately and individualize treatment plans accordingly
      vi. Evaluate need for postpartum prophylaxis

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**Prevention of PP Guidelines**

I. **Guidelines**
   a. Available only in the United Kingdom
   b. National Institute for Health and Clinical Excellence (NICE)
      i. Same care as that for anyone with a mental illness
      ii. Discussion of treatment options, including risks and benefits of pharmacotherapy versus untreated mental illness
      iii. Start at lowest effective dose, slowly increase, favor monotherapy
   c. Scottish Intercollegiate Guidelines Network (SIGN)
      i. Same care as that for anyone with mental illness, using those with less evidence of adverse effects
      ii. Evidence is not of sufficient quality to support a recommendation
      iii. Women who have been treated with effective prophylaxis for psychotic disorder should have prophylactic treatment reinstated after birth
d. American College of Obstetricians and Gynecology
   i. Evidence on risks and benefits of treatment for certain psychiatric illnesses during pregnancy
   ii. Appraisal of the clinical consequences of offspring exposure, the potential effect of untreated maternal psychiatric illness, and the available alternative therapies

### Clinical Question and Literature Review

#### I. Which pharmacologic agents are effective to prevent PP while balancing the risks and benefits of pharmacotherapy during pregnancy?

#### II. Studies for review


#### Overview

<table>
<thead>
<tr>
<th>Purpose</th>
<th>Examine the research evidence on interventions for the prevention and treatment of PP (<em>Appendix B</em>)</th>
</tr>
</thead>
</table>
| Results for Prevention using Li/CBZ | Prophylactic Li was supported in five studies  
- May decrease the rate of relapse from approximately 50% to less than 22%  
- Prophylactic CBZ was supported in two studies |
| Conclusion | Li was most commonly studied approach showing efficacy  
- Further support from studies demonstrating high relapse rates among women who discontinue their Li during pregnancy  
- Insufficient evidence to suggest whether Li is equally effective when administered prophylactically through pregnancy or started immediately in the postpartum period  
- CBZ may be effective, but teratogenic risk may outweigh benefit |
| Limitations | Methodological quality differed significantly, resulting in a limited evidence base to guide current practice and decision making  
- Study sample sizes were generally small, reports were often retrospective, and the designs were primarily case reports  
- The diagnostic measures were diverse, making comparisons difficult  
- Studies represent a variety of prevention approaches in various combinations, further precluding any clear comparisons between studies |
## Overview

### Purpose

Compare Li use during pregnancy to its initiation postpartum in women at high risk for PP.

### Design

Naturalistic

### Patients

- History of BPD I/II or PP without manic or psychotic symptoms outside postpartum period

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**Figure 3: Women at High Risk of Postpartum Psychosis Included in Prevention Study**

- Psychotic disorders such as schizophrenia or schizoaffective disorder

### Exclusion

- Postpartum relapse, defined as the occurrence of any psychiatric episode fulfilling the DSM-IV criteria, including hypomanic episodes

### Methods

- Women already taking maintenance Li were advised to continue treatment
  - Maintenance Li treatment
  - Dosed three times a day during pregnancy
  - After delivery, dosed once per day
  - Target minimum plasma level postpartum of 0.8 mmol/L
- High-risk women who were clinically stable and medication free at the time of evaluation were advised to start Li prophylaxis immediately postpartum
  - Li was started the first evening after delivery
  - Dosed once daily according to the plasma level
  - Target minimum of 0.8 mmol/L
  - Plasma Li levels were monitored twice weekly during the first week postpartum, once per week during weeks 2 and 3, and thereafter as indicated

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Methods, continued
- Spent first week in private room, where nurses performed the overnight newborn feedings to help mothers sleep
- Benzodiazepine (lorazepam, 1 mg at bedtime) to help sleep
- Advised against breast-feeding

Statistical analysis
- Characteristics of the study group
- Categorical data were evaluated by means of Fisher’s exact test
- Continuous variables were examined with two-sample t tests
- Categorical outcomes related to relapse risk were examined by using both Fisher’s exact test and odds ratios with corresponding 95% confidence intervals (CIs)

Results

Baseline characteristics
- No significant differences were found in age, education, marital status, unplanned pregnancy, smoking during pregnancy, or the frequency of Cesarean section

<table>
<thead>
<tr>
<th>Table 5: Baseline Characteristics with Significant Differences</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variable</td>
</tr>
<tr>
<td>Previous pregnancy</td>
</tr>
<tr>
<td>Previous delivery</td>
</tr>
</tbody>
</table>

Results

Figure 4: Cumulative Incidence of Relapse During Pregnancy and the Postpartum Period in Women with Bipolar Disorder or a History of PP
- The timing of relapse was substantially different between the women with BPD and those with PP only
- Despite being medication free throughout the entire pregnancy, none of the 29 women with PP relapsed during pregnancy
- Postpartum, four of the 29 (13.8%) relapsed
- Of the women with BPD (n=41), 24.4% relapsed during pregnancy, despite prophylaxis use by the majority throughout pregnancy
### Table 6: Characteristics of Women with Relapse

<table>
<thead>
<tr>
<th>Population</th>
<th>Relapse during pregnancy n (%)</th>
<th>Postpartum relapse n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BPD (n=41)</td>
<td>10 (24.4%)</td>
<td>9 (22.0%)*</td>
</tr>
<tr>
<td>History of both postpartum and non-postpartum episodes (n=8)</td>
<td></td>
<td>4 (50%)</td>
</tr>
<tr>
<td>History of only non-postpartum episode (n=33)</td>
<td></td>
<td>9 (27.3%)</td>
</tr>
<tr>
<td>PP (n=29)</td>
<td>0</td>
<td>4 (13.8%)</td>
</tr>
<tr>
<td>P value</td>
<td>&lt;0.01</td>
<td></td>
</tr>
</tbody>
</table>

* 6 out of 9 had relapsed during pregnancy, which therefore was a significant risk factor for relapse postpartum (p<0.01, Fisher's exact test; odds ratio=14.0, 95% CI=2.5–80.0)

- Relapse in the women with BPD, both during pregnancy and postpartum, was especially common in women with a history of postpartum episode

### Table 7: Relation of Prophylaxis with Relapse

<table>
<thead>
<tr>
<th>Time period and group</th>
<th>BPD (n=41)</th>
<th>History of PP (n=29)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total n (%)</td>
<td>Relapse n (%)</td>
</tr>
<tr>
<td>Pregnancy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prophylaxis</td>
<td>31 (75.6%)*</td>
<td>6 (19.4%)</td>
</tr>
<tr>
<td>No prophylaxis</td>
<td>10 (24.4%)</td>
<td>4 (40%)</td>
</tr>
<tr>
<td>Postpartum</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prophylaxis</td>
<td>26 (63.4%)</td>
<td>2 (7.7%)</td>
</tr>
<tr>
<td>Stable pregnancy</td>
<td>10 (24.4%)</td>
<td>6 (60%)</td>
</tr>
<tr>
<td>Unstable pregnancy</td>
<td>16 (36%)</td>
<td></td>
</tr>
<tr>
<td>No prophylaxis</td>
<td>5 (12.2%)</td>
<td>1 (20%)</td>
</tr>
</tbody>
</table>

*27 used Li, two used Li plus an antidepressant, one used Li plus an antipsychotic, and one used haloperidol monotherapy

**17 used Li and 3 used antipsychotics

- Postpartum relapse rate was highest in women with BPD who experienced mood episodes during pregnancy (60%)
- None of the 20 women with a history of PP only who used prophylaxis relapsed, compared to 44.4% of patients with PP only who declined prophylaxis
Conclusions

Author's Conclusions

- Findings suggest that postpartum prophylaxis is highly efficacious in women at high risk for PP who do not have a diagnosis of BPD
- Women with a history of PP but without manic or psychotic symptoms outside the postpartum period may not require prophylaxis during pregnancy
- The authors recommend initiating prophylactic treatment immediately postpartum in women with a history of psychosis limited to the postpartum period, to avoid in utero fetal exposure
- Patients with BPD require continuous prophylaxis throughout pregnancy and the postpartum period to reduce postpartum relapse risk
- Benefits of continuous Li use, both during pregnancy and postpartum, must be carefully weighed against the teratogenic effects
- Benefits of postpartum prophylactic treatment with Li must be considered in light of the relative risk to infants of breast-feeding exposure versus the loss of the benefits of breast-feeding

Strengths

- Identified a clinically relevant algorithm that may prove useful in determining prophylaxis requirements
- This algorithm may help reduce the fetal risk that can accompany in utero exposure to medications without compromising the efficacy of postpartum prophylaxis

Limitations

- Likely missed symptoms associated with transient instability, as study was principally designed to detect mood episodes fulfilling DSM-IV criteria
- Naturalistic design, leaving open the possibility that some of the outcomes were influenced by patients’ preferences

Overview


Purpose

- To evaluate the efficacy of divalproex to prevent episode recurrence in postpartum women with bipolar disorder

Design

- Single-blind, non-randomized

Patients

- Pregnant
- < 35 weeks’ gestation
- Aged 21–45 years
- DSM-IV diagnosis of BPD I/II
- No medical conditions that precluded divalproex use, normal liver function, thyroid studies, and complete blood count
- Identified obstetric and pediatric care providers

Outcomes

- Remission – not having an episode of depression, mania, or hypomania

Methods

- Several phases over 15-month period
- Clinical trial began immediately postpartum
- Recruited during pregnancy and given choice of two treatment plans during postpartum period
  - Monitoring without medication
  - Monitoring plus divalproex
- Monitoring protocol included psychoeducation, weekly mood symptom assessments
**Treatment options**

- Postpartum monitoring alone
  - Goal: observation for affective symptoms with rapid treatment if symptoms recurred
  - Mood symptom ratings done by the independent evaluator (mood rater), who was blind to condition choice as well as to protocol design and hypotheses
  - Symptom scales: Hamilton Rating Scale for Depression (HRSD), Bech-Rafaelson Mania Scale (BRMS) or Mania Rating Scale (MRS), Global Assessment of Function (GAF)
  - The subject was assessed each week for 20 weeks
- Monitoring plus divalproex
  - Divalproex started at 250 mg twice a day, increased to serum levels of 50-100 mg/L
  - Patient assessed weekly for 20 weeks, either in person or by phone
  - Administered through first 17 weeks postpartum to cover highest risk period
  - Divalproex discontinued during weeks 17-20 if the patient elected to do so, titrated down by 33% per week

**Endpoints**

- Independent evaluator determined whether the subject met DSM-IV criteria for an episode
  - If the patient met DSM-IV criteria, she reached the study end point for recurrence
- Withdrawn from study if:
  - Did not take their first dose of medication within 48 hours of birth
  - Did not complete treatment
  - Did not take medication for 3 consecutive days or more than 10 days total
  - Missed a total of three phone or in-person assessment sessions

**Statistical Analysis**

- Initial comparisons of demographic and history variables between conditions were completed with t-tests or chi-squared tests
- The rates of diagnostic episode end point occurrence (depression, hypomania, or mixed episodes) were compared with Fisher exact tests
- Exact log-rank tests were applied for evaluation of time to first episode (any type) of recurrence
- Mann–Whitney U scores were used to compare the percentages of weeks that subjects were well across the study

**Results**

**Baseline characteristics**

- No significant demographic differences were found (age, married, socioeconomic status, previous births, diagnosis, substance abuse, previous hospitalizations, GAF score)
- Significant difference found for clinical history - women who had previous suicide attempts were significantly more likely to select the divalproex + monitoring option

<table>
<thead>
<tr>
<th>Variable</th>
<th>Divalproex + monitoring (n=15, 58%)</th>
<th>Monitoring only (n=11, 42%)</th>
<th>Difference (p value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous suicide attempts</td>
<td>5 (33%)</td>
<td>0 (0%)</td>
<td>0.05</td>
</tr>
</tbody>
</table>
Results

- Compliance
  - 8/15 had serum levels >50mg/L at every test date
  - 2 had <50 mg/L only once
  - 3 had <50mg/L on more than 20% of test dates, usually due to dose restrictions from side effects
- Dose of divalproex ranged from 250 to 1500 mg/day
- No significant differences between groups in the proportions of women who developed postpartum hypomania/mania, depression, or mixed-state diagnoses
- 18/26 (69%) of women had recurrence
- Time to development of episodes of different types also did not vary between groups
- No significant difference in serum levels between those who had episode and those who did not (recurrence, 71mg/L; remained well; 66mg/L)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Medication group (n=15)</th>
<th>Monitoring only group (n=11)</th>
<th>Difference (p value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Completed trial without episode</td>
<td>5 (33%)</td>
<td>3 (27%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Recurrence</td>
<td>10 (67%)</td>
<td>8 (73%)</td>
<td></td>
</tr>
</tbody>
</table>

Conclusions

Author’s Conclusions

- Divalproex was not significantly more effective than monitoring alone
- Comparison of the relative efficacy of Li and divalproex is problematic due to varying study design
- Aspects of the study increased the likelihood of early identification of an episode of any polarity

Strengths

- Independent mood rater blind to study design
- Standard scales to measure symptoms of mania and depression longitudinally
- Serial drug levels as measures of compliance
- Prospective weekly postpartum assessments

Limitations

- Women selected the treatment condition to which they were assigned
- Small cohort, non-random assignment
Overview

Purpose
To review the efficacy of olanzapine in the prevention of PP in women with BPD

Design
Naturalistic, prospective

Patients
Non-random, convenience sample
Diagnosis of BPD I or II recruited during first trimester

Outcomes
Development of PP according to the DSM-IV criteria as a major depressive, manic, or mixed episode with psychotic features within 4 weeks of delivery

Methods
Seen for a total of 9 visits, 3 during pregnancy (once every trimester), 6 after delivery, including visits 1 week and 1 month after childbirth
Diagnostic interview using Schedule for Affective Disorders and Schizophrenia
HRSD and MRS were used to evaluate mood episodes
Women rated their mood in Personal Mood Diary, also kept a record of quality of sleep

Treatment
Olanzapine 5-10 mg starting the night of delivery – recommended to women who were not on any medication at time of delivery
If patient had poor tolerability or an inadequate response to olanzapine, additional medications were used depending on the nature, severity, and polarity of the index episode
Women who declined to take OLZ were prescribed the same drugs they had taken with benefit in the past.
Avoidance of sleep disruption and rooming out of the newborn
Stimulus reduction by limiting the number of visitors was suggested to help in post-delivery sleep

Statistical Analyses
Fischer’s exact test to determine difference between groups

Results
Baseline characteristics
No significant differences between groups for diagnosis, parity, sex of infant, presence or absence of previous PP, previous hospitalization, family history of mood disorders/BPD, age

Results

Table 10: Emergence of Episodes

<table>
<thead>
<tr>
<th>Variable</th>
<th>Olanzapine (n=11)</th>
<th>No olanzapine (n=14)**</th>
<th>Difference (p value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Episode</td>
<td>2 (18.2%)*</td>
<td>8 (57.1%)</td>
<td>0.099</td>
</tr>
</tbody>
</table>

*2/11 in olanzapine group received combination (one with trazodone, one with Li)
**No olanzapine group included no treatment (n=8), Li (n=2), paroxetine (n=2), venlafaxine (n=1)

6/8 (62.5%) of multiparous women in olanzapine group had history of PP, but none experienced PP with olanzapine treatment
Olanzapine group episodes – both were depression
No olanzapine group episodes – 4 depression, 2 PP, 1 mixed, 1 hypomania
Conclusions

Author’s Conclusions
- Efficacy with olanzapine has been demonstrated, further evidence is required
- Robust data in non-postpartum samples must be considered

Strengths
- First study using an antipsychotic for the prevention of PP

Limitations
- Used in combination with other drugs
- Behavioral interventions should not be underestimated
- Sedative effect of olanzapine may play a role in reducing relapse rate
- Close monitoring of the mood state may have allowed early detection
- Small cohort, non-random assignment, short evaluation period


Hormone therapy
- Three studies reported the effects of hormone therapy for the prevention of PP
- There are mixed findings for the preventative effects of estrogen
- No evidence to support the prophylactic use of progesterone

Table 11: Effectiveness of Hormone Therapy in the Prevention of PP

<table>
<thead>
<tr>
<th>Study</th>
<th>Participants</th>
<th>Intervention</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sichel et al. 1995, open clinical trial</td>
<td>11 women with history of PP (n=7) or postpartum depression (n=4)</td>
<td>Prophylactic oral estrogen (5 mg, bid) immediately after delivery (dose reduced over 4 week). 2/11 also received IV estrogen to ensure compliance for 2 days</td>
<td>1/11 (9%) relapsed at the one-year follow-up (non-compliance) Onset of relapse was 1 week postpartum</td>
</tr>
</tbody>
</table>

Conclusion
- Evidence base is poor
- Insufficient evidence to support their use

Strengths
- Provides evidence in support of “estrogen withdrawal state” theory of PP

Limitations
- Small cohort, non-random assignment
- No evidence demonstrating efficacy in mood disorders more generally
Summary and Recommendations

I. Medications
   a. Mood stabilizers
      i. Li
         1. Consistently showed effectiveness
         2. Relapse rates increase with withdrawal of prophylaxis
         3. Timing remains controversial
      ii. CBZ
         1. May be effective, limited data
         2. Teratogenic risk may outweigh benefit, recommend an alternative mood stabilizer
      iii. Divalproex
         1. Evidence does not suggest effectiveness
         2. Limited evidence
   b. Antipsychotics
      i. Olanzapine may be effective, though limited data
      ii. Other antipsychotics may be useful given effectiveness in general mood disorders, but no evidence for prevention of PP
   c. Hormone Therapy
      i. Some studies have shown effectiveness of estrogen, though insufficient evidence to support use
      ii. No evidence to support effectiveness of progesterone
      iii. No evidence of effectiveness in general mood disorders limits use

II. PP summary
   a. Diagnosis is not clearly defined in DSM-IV, however, it is a psychiatric emergency and prevention is critical
   b. History of BPD and history of PP are the greatest risk factors
   c. Mood stabilizers, antipsychotics, and hormone therapy have all been studied
      i. Li consistently shows greatest efficacy and has the most data
      ii. Weigh risks and benefits of all pharmacologic agents
         1. Risk of untreated PP to both mother, fetus and family
         2. Risk of pharmacotherapy to fetus
         3. Risk while breast-feeding, including risk of not breast-feeding

III. Evidence-based recommendations
   a. Psychosocial interventions
   b. Prophylaxis during planned pregnancy
      i. Women with BPD with severe illness
         ii. Continue with medication that patient is stable on
            1. Lowest dose
            2. Monotherapy
            3. Avoid CBZ and divalproex
            4. Li may be considered
      iii. Low threshold for reinitiation of pharmacotherapy
   c. Prophylaxis immediately following delivery
      i. All women with BPD
      ii. History of PP only
      iii. Li
References


Appendix A:

Table 12: Other Pharmacologic Agents for the Treatment of PP\textsuperscript{13,20,33}

<table>
<thead>
<tr>
<th>Drug</th>
<th>Proposed Mechanism of Action</th>
<th>Risk in pregnancy</th>
<th>Pregnancy category</th>
</tr>
</thead>
</table>
| Lamotrigine                 | Unknown, thought to inhibit voltage-sensitive sodium channels, thereby stabilizing neuronal membranes and modulating release of excitatory amino acids | • Midline facial clefts, possibly with doses >200 mg/day  
• Stevens-Johnsons syndrome  
• Hepatotoxicity  
• Efficacy studies lacking in pregnancy  
• Secreted in breast milk | C |
| First generation antipsychotics | DA antagonism                                                                                 | • No significant teratogenic effects  
• Secreted in breast milk | C |
| Second generation antipsychotics | Combination of DA and 5HT\textsubscript{2} antagonism                                           | • Little evidence, therefore not recommended  
• Metabolic syndrome, gestational diabetes  
• Secreted in breast milk | C |
| Electroconvulsive therapy (ECT) | Unknown, thought to boost neurotransmission                                                     | • Uterine contractions  
• Congenital malformations  
• Few side effects, may pose lower risks than pharmacotherapy | |

Appendix B:

Table 13: Effectiveness of Li and/or CBZ in the Prevention of PP

<table>
<thead>
<tr>
<th>Study</th>
<th>Participants</th>
<th>Prophylaxis</th>
<th>Within 3 months</th>
<th>Treatment group:</th>
<th>Treatment group:</th>
<th>No treatment:</th>
<th>No treatment:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Austin 1992, retrospective study\textsuperscript{34}</td>
<td>17 women with BPD or history of PP</td>
<td>Li (serum levels of ( \geq 0.4 ) mmol/L during pregnancy (7/9) or within 48 h following delivery (2/9)</td>
<td>Within 3 months</td>
<td>2/9 (22%) relapsed</td>
<td>6/8 (75%) relapsed</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Cohen et al. 1995 retrospective study\textsuperscript{35} | 27 women with BPD, 4/27 had history of PP                                  | 14 various combinations  
• Li alone = 9  
• Li + CBZ = 2  
• Li + antidepressant = 2  
• CBZ = 1  
• Doses not specified | Within 3 months                  | 1/14 (7%) relapsed             | 8/13 (62%) relapsed, (RR 8.6)    |             |          |
| Stewart 1988, case series\textsuperscript{36} | 4 women with history of PP, 3/4 BPD                                         | Prophylactic Li (900–1,200 mg/day) immediately following delivery           | • No reported relapses, maintained at 6 month follow-up |                |                  |             |          |
### Results from Systematic Review for Treatment of PP

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ECT</strong></td>
<td>Three studies&lt;br&gt;The limited evidence supports the use of ECT in the treatment of PP when administered alone as well as when combined with the antipsychotic chlorpromazine</td>
</tr>
<tr>
<td><strong>Antipsychotics</strong></td>
<td>Four studies - successful treatment with chlorpromazine, clozapine, and pimozide&lt;br&gt;The use of antipsychotics in the treatment of PP requires further investigation before any conclusions can be drawn about their effectiveness postnatally&lt;br&gt;Their use at this time, however, must be considered in light of the large body of evidence of efficacy in nonpostpartum episodes</td>
</tr>
<tr>
<td><strong>Mood stabilizers</strong></td>
<td>Three studies – Li&lt;br&gt;Found to be effective in one case study where it was used as monotherapy and in two studies where it was used as adjunct therapy&lt;br&gt;Further comparative investigations are needed that examine whether the effects of Li are equally effective in treating episodes of PP</td>
</tr>
<tr>
<td><strong>Hormones</strong></td>
<td>Five studies&lt;br&gt;With only a few individual case reports, it is not possible at present to conclude that any evidence exists for the hormonal treatment of PP&lt;br&gt;Insufficient research to recommend&lt;br&gt;Preliminary results would suggest that further studies are indicated</td>
</tr>
<tr>
<td><strong>Propranolol</strong></td>
<td>Two studies have supported the effects of propranolol&lt;br&gt;Women treated with propranolol were discharged sooner than those treated with chlorpromazine (61 days compared to 104 days), symptoms improved more rapidly (3 days compared to 55 days)</td>
</tr>
</tbody>
</table>

### Stewart et al. 1991, open clinical trial<sup>37</sup>

- 21 women with history of PP (included 3 women from Austin et al.)
- Prophylactic Li (750–1,200 mg/day) at 34-week gestation (5/21) or within 24 h after delivery (16/21)
- 2/21 (10%) relapsed within 8 days postpartum, both mild
- No other relapse at 6 months

### Van Gent and Verhoeven 1992, prospective 3 center study<sup>38</sup>

- 11 women with history of BPD, 16 pregnancies (5 with 2 pregnancies)
- Prophylactic Li (serum levels ≥ 0.7 mmol/L) = 8<br>CBZ=2 Haloperidol=1<br>Refused treatment = 5
- Within 3 months<br>**Treatment group:** 3/11 (27%) had manic/psychotic relapse<br>**No treatment:** 3/5 (60%) relapsed (refused treatment)