* Psychotropic drugs during breastfeeding: Focus on bipolar disorder

Isabella Pacchiarotti, M.D., Ph.D.
Breastfeeding is recommended by the American College of Obstetricians and Gynecologists, the American Academy of Pediatrics, and the WHO.

The latter recommends exclusive breastfeeding for at least the first 6 months postpartum and for at least two years in association with complementary food.

Breast-fed infants show enhanced cognitive development, protection against infections, and reduced risk of sudden infant death syndrome (Hauck et al., 2011; American Academy of Pediatrics, 2012).

Furthermore, mothers who breast-fed their infants are protected against both breast and ovarian cancer (American Academy of Pediatrics, 2012).
Pregnancy and motherhood reset many brain functions in both mothers and fathers.

52% of women with an existing diagnosis of BD are likely to manifest mood symptoms during postpartum (Viguera et al., 2011).

29% of women with BD are at risk for hospitalization within one year from delivery (Munk-Olsen et al., 2009).

On the other hand, women stopping or changing medication are at a higher risk for relapse of BD (Viguera et al., 2000, 2007, 2011).
Hence, caution is needed when using or discontinuing drugs in breastfeeding women.

For these reasons, medication during lactation should be carefully balanced to avoid damaging the infant’s or the mother’s health.

We decided to undertake the task of assessing the risk for lactating infants when their mothers take drugs usually administered for bipolar disorder.
To perform our PRISMA review (Moher et al., 2009) we used the following search strategy:

* ((lactation OR breast feeding OR postpartum)) AND (antidepressant agents OR antipsychotic agents OR lithium OR valproic acid OR carbamazepine OR lamotrigine OR topiramate OR gabapentin OR oxcarbamazepine OR benzodiazepines OR pregabalin OR modafinil OR pramipexole OR anticonvulsivants OR antiepileptic drugs OR valproate OR atypical antipsychotic drugs OR typical antipsychotic drugs OR tricyclic antidepressant OR serotonin reuptake inhibitor OR desvenlafaxine OR agomelatine OR haloperidol OR chlorpromazine OR clozapine OR risperidone OR olanzapine OR quetiapine OR ziprasidone OR aripiprazole OR paliperidone OR lurasidone OR asenapine OR iloperidone OR serotonin-norepinephrine reuptake inhibitor OR noradrenergic and specific serotonin antidepressant OR norepinephrine reuptake inhibitor OR fluoxetine OR paroxetine OR sertraline OR citalopram OR escitalopram OR fluvoxamine OR venlafaxine OR mirtazapine OR reboxetine OR duloxetine OR bupropion OR trazodone OR nefazodone OR vilazodone)
* Additionally, we searched the following databases:

* **Cochrane library**
  * Strategy: *(lactation OR breast feeding) AND (mood stabilizer OR antipsychotic OR antidepressant)*

* **EMBASE**
  * Keywords: *lactation, bipolar disorder and treatment*

* **clinicaltrials.gov**
  * Keywords: *lactation, bipolar disorder and treatment*
* Systematic searches were performed by two blind independent researchers (IP and JL)
Inclusion criterion: Paper clearly reporting estimated drug amount or effects on infants and children exposed to anti-BD drugs during breastfeeding - English

Search: (lactation OR breastfeeding) AND (mood stabilizer* OR antipsychotic* OR antidepressant* [and individual drugs in PubMed])

1548 records

21 duplicates

1527 records

1315 not eligible

212 records

16 inaccessible

161 records

35 unrelated to aims

Final selection

31 lithium/mood stabilizers
25 antipsychotics
86 antidepressants
19 “other drugs”
Drugs are absorbed and pass into the blood stream; in the breast, they diffuse passively from breast capillaries in the mammary duct and passed in milk:

- Bioavailability
- Liposolubility
- Binding protein
- GI maturation
- M/P ratio
- Relative infant dose
- Frequency of feedings
- Premature and newborn
- Infant stability
Drugs and Breastfeeding: V. Psychotropic drugs used in BD and compatibility with breast feeding
Drugs and Breastfeeding:
I. Lithium and anticonvulsant stabilisers
<table>
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<tr>
<th>Drug</th>
<th>Efficacy/Safety in BD</th>
<th>Safety profile during Breastfeeding</th>
<th>Recommendations</th>
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</table>
| Lithium | • Manic episode  
• Prophylaxis of BD  
• Suicide prevention               | • Breastfeeding could be permitted with lithium through an individualized approach  
• Maternal lithium doses should be kept as low as possible  
• *Moderately safe*                  | • Educate mothers/parents to a careful observation of exposed infants (muscle tone, tremor, dehydration, lethargy, feeding problems, weight gain)  
• Frequent monitoring of the infant’s renal and thyroid function  
• Obtain maternal and infant serum lithium levels if clinical concerns arise |
<table>
<thead>
<tr>
<th>Specific drugs</th>
<th>Efficacy/Safety in BD</th>
<th>Safety profile during breastfeeding</th>
<th>Recommendations</th>
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<tbody>
<tr>
<td><strong>Anticonvulsants</strong></td>
<td></td>
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<tr>
<td>Anticonvulsants</td>
<td>The choice of an antiepileptic during breastfeeding is primarily determined by the effectiveness according to the type or phase of BD. With a careful monitoring of the baby, monotherapy with one AED does not excluded exclusive breastfeeding, since there are no serious indications that breastfeeding during AED treatment leads to developmental disorders in the child.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Valproate</td>
<td>Manic/mixed episode • Prophylaxis of BD</td>
<td>With a close observation for possible side-effects, the infant can be breastfed • Safe</td>
<td>Thrombocytes count and liver enzymes</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>Prophylaxis of depressive recurrences in BD</td>
<td>Although most of the breastfed children showed no symptoms, breastfeeding with LTG need to be considered by individual cases due to the variable transfer of this drug to the child and accumulation • Moderately safe</td>
<td>It is advisable to check the presence of thrombocytosis and rush in the nursing infant. • The lowest dose should be prescribed (up to 200mg/day)</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>- Manic episode • - Prophylaxis of BD</td>
<td>With a close observation for possible side-effects, he infant can be breastfed • Safe</td>
<td>Total and differential leukocyte count</td>
</tr>
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Drugs and Breastfeeding: II. Antipsychotic drugs
### Antipsychotics

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</table>
| **Antipsychotics**  | • In general, APs may be used during breastfeeding, since the relative infant dose is in the range of 0-2% for most of them and side-effects in breast-fed infants are only described exceptionally  
• Monotherapy should be the goal and should be maintained as low as possible  
• Educate mothers/parents to a careful observation of exposed infants |                                                                                                      |                                      |
| Quetiapine          | • Manic/mixed episode  
• Bipolar depression  
• Prophylaxis of BD | • First line treatment in BD during breastfeeding.  
• *Safe* | Infant monitoring |
| Olanzapine          | • Manic/mixed episode  
• Prophylaxis of BD | • First line treatment in BD during breastfeeding.  
• *Safe* | Infant monitoring |
| Risperidone         | • Manic/mixed episode | • Possible for breastfeeding under medical supervision  
• *Another AP should be preferred (few data)* | Infant monitoring |
| Haloperidol         | • Manic/mixed episode | • Possible for breastfeeding under medical supervision  
• *Another AP should be preferred (few data)* | Infant monitoring |
| Aripiprazole        | • Manic/mixed episode | • Not recommended due to insufficient data |                                      |
| Lurasidone          | • Bipolar depression (FDA) | • Not recommended due to lack of data |                                      |
| Ziprasidone         | • Manic/mixed episode  
• Prophylaxis of BD as adjunctive treatment | • Not recommended due to insufficient data |                                      |
| Asenapine           | • Manic/mixed episode | • Not recommended due to lack of data |                                      |
| Loxapine            | • Agitation in BD | • Not recommended due to lack of data |                                      |
Drugs and Breastfeeding: III. Antidepressant drugs
### Antidepressants

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<th>Efficacy/Safety in BD, during breastfeeding, and Recommendations</th>
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| **Antidepressants** | • None of the available ADs is officially indicated for bipolar depression  
  • AD monotherapy should be avoided in postpartum BD depressive episode  
  • BD women with depression starting ADs should be closely monitored for signs of hypomania or mania and increased psychomotor agitation, in which case ADs should be discontinued |
| **SSRIs** | • Sertraline and paroxetine are first choice during breastfeeding for infant safety  
  • Fluoxetine and citalopram are less recommended; monitoring is required due to possible accumulation and symptom onset in nursing infants  
  • Escitalopram and fluvoxamine are not recommended due to insufficient data |
| **SNRIs** | • Venlafaxine: not recommended due to its quite high relative infant dose. If venlafaxine is continued during breastfeeding, nursing infants, especially newborn or preterm, should be monitored for excessive sedation and adequate weight gain  
  • Duloxetine: A better-studied alternative may be preferred, especially while nursing a newborn or preterm infant |
| **Bupropion** | • Another drug may be preferred, especially while nursing a newborn or preterm infant. Exclusively breastfed infants should be monitored if mother takes bupropion during lactation, possibly including serum level measurement |
| **TCAs** | • Amitriptyline and nortriptyline have a better safety profile during lactation |
| **Mirtazapine** | • Due to inadequate data, mirtazapine and mianserin are not recommended |
Drugs and Breastfeeding: IV. ‘Other Drugs’
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| Benzodiazepines | • Maternal use of benzodiazepine during breastfeeding is generally acceptable, provided that the infants are monitored for adverse CNS effects | • Clonazepam, lorazepam, and diazepam should be considered as first line treatment  
• *Safe* | • Benzodiazepines should be prescribed at the lowest doses and only for short periods  
• Parents must be educated to carefully evaluate exposed infants (sedation, weak suckling and restlessness)  
• Particular attention should be paid to any symptoms of withdrawal in the breastfed infant in case of discontinuation of BDZs |
|                | • Anxiety and insomnia in BD |                                   |                |

*Benzodiazepine anti-anxiety agents*
* Medications found to be effective during pregnancy should be considered for use in postpartum.
* For BD women who received no medication during pregnancy, previously effective medications should be given priority.
* In BD with postpartum onset, care should be given to the compatibility of the drug with breastfeeding and to its efficacy in treating the bipolar episode.
* During treatment with any psychotropic drug, infants should be monitored for persistent irritability, sedation, and feeding or failure to thrive.
* Most psychotropic drugs used to treat BD are not contraindicated during breastfeeding

* Lithium is no longer believed to be dangerous as previously thought

* Carbamazepine and valproate are quite safe during lactation

* Lamotrigine (LTG) needs to be used at the lowest doses

* Among antipsychotics, quetiapine and olanzapine are quite safe, while risperidone needs constant medical supervision during breastfeeding; clozapine and amisulpiride are contraindicated
* ADs bear the risk of hypomanic, manic or mixed switches, especially if used alone

* SSRIs, especially sertraline and paroxetine, have the best safety profile during lactation, combined with low mood switch likelihood; care is needed when administering fluoxetine during lactation, to avoid accumulation

* Bupropion and mirtazapine have insufficient data
* TCAs are quite safe, but their use should be balanced against their unfavourable adverse events profile and their mood switch likelihood

* Clonazepam, lorazepam and diazepam are best among BZDs, but their use should be short-term and accompanied by carefully assessing symptoms in exposed infants

* Other drugs used for BD have insufficient documentation during lactation
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Gracias!