Prescribing antipsychotics and mood stabilizers in pregnancy and breastfeeding

Angelika Wieck
<table>
<thead>
<tr>
<th>Timing</th>
<th>Potential Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early pregnancy</td>
<td>Major structural defects</td>
</tr>
<tr>
<td>Later pregnancy</td>
<td>Minor structural defects, functional defects, premature delivery, abnormal fetal growth</td>
</tr>
<tr>
<td>Pre-delivery</td>
<td>Neonatal toxicity, neonatal withdrawal</td>
</tr>
<tr>
<td>Timing mostly uncertain</td>
<td>Intelligence, behaviour, motor and social development</td>
</tr>
</tbody>
</table>
Why are the safety data for psychotropics so difficult to interpret?

No RCT’s
+ Retrospective data
+ Small sample sizes
+ Non-psychiatric patients
+ Multiple testing
+ Increased vigilance if mother takes psychotropics
+ Little information on severity of malformations

Myriad of (other) confounding factors!
Main Confounding Factors

- Maternal mental illness
- Parental Genes
- Obesity
- Diabetes
- Phys. illness
- Stress
- Low income
- Street drugs
- Smoking
- Alcohol
- Pregnancy & child outcome

Psychotropic medication

Grote et al, Arch Gen Psychiatry. 2010; 67:1012-24
Major congenital malformations by BMI

Swedish Population Study, > 1.2 million births

<table>
<thead>
<tr>
<th>BMI (kg/m²)</th>
<th>Events (%)</th>
<th>Adjusted risk ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>43 550 (3.5)</td>
<td></td>
</tr>
<tr>
<td>&lt;18.5</td>
<td>1020 (3.4)</td>
<td>1.01 (0.95 to 1.08)</td>
</tr>
<tr>
<td>18.5 to &lt;25</td>
<td>25 713 (3.4)</td>
<td>1.00 (ref)</td>
</tr>
<tr>
<td>25 to &lt;30</td>
<td>11 050 (3.5)</td>
<td>1.05 (1.02 to 1.07)</td>
</tr>
<tr>
<td>30 to &lt;35</td>
<td>3903 (3.8)</td>
<td>1.12 (1.08 to 1.15)</td>
</tr>
<tr>
<td>35 to &lt;40</td>
<td>1335 (4.2)</td>
<td>1.23 (1.17 to 1.30)</td>
</tr>
<tr>
<td>≥40</td>
<td>529 (4.7)</td>
<td>1.37 (1.26 to 1.49)</td>
</tr>
</tbody>
</table>

Progressive increase of malformations of the:

- Heart
- CNS
- Limbs

Cigarette smoking in pregnancy – Increased risk of congenital

- Heart defects
- Oro-facial clefts
- Neural tube defects
Antipsychotic Drugs
Congenital anomalies

Study with largest number of exposures and confounding factors controlled for\(^1\)

- 1.3 million women enrolled in Medicaid, US
- N= 9,991 first trimester exposures

Any MCM

- **Overall malformations**: RR 1.26; 95%, CI 1.02-1.56
- **Cardiac MCMs** at doses > 2mg: RR 2.08, 95% CI 1.32-3.28

Is the risk of gestational diabetes increased? - Medicaid cohort study -

- Women who discontinued APs before pregnancy vs women who continued in first 20 weeks of pregnancy
- N: 2,872 continued, 7,507 discontinued
- Range of confounders taken into account

<table>
<thead>
<tr>
<th></th>
<th>Adjusted RR</th>
<th>Conf. Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aripiprazole</td>
<td>0.82</td>
<td>0.5-1.32</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>0.76</td>
<td>0.29-2.00</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>1.28</td>
<td>1.01-1.62</td>
</tr>
<tr>
<td>Risperidone</td>
<td>1.09</td>
<td>0.7-1.70</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>1.61</td>
<td>1.13-2.29</td>
</tr>
</tbody>
</table>

Neurodevelopment¹

- 2,934 children and 9 cohort studies
- Poor methodology
- Most controls were children of mothers with no psychiatric illness
- Most consistent finding was transient delay in motor development

https://doi.org/10.1007/s00787-018-1177-1
Summary for antipsychotics in pregnancy

• Current evidence suggests that antipsychotics are not major teratogens

• Small increase in anomalies after higher dose risperidone? Requires further study

• Some antipsychotic may cause gestational diabetes, evidence is strongest for olanzapine and quetiapine

• Every woman taking an antipsychotic should have an oral glucose tolerance test (at 26 weeks)

• No evidence for lasting neurodevelopmental effects

• No or very few data on newer antipsychotics (paliperidone, asenapine, lurasidone, capripazine)
Plasma levels of antipsychotics
during pregnancy compared to pre- and postnatal
(in the same women)

1Westin et al (2018), Clin Pharm Therap 103, 477-484
When should we measure quetiapine or aripiprazole levels in the perinatal context?

- In women planning a pregnancy
- In all women in pregnancy and early postpartum

+ Close monitoring of mental state
Anti-epileptic drugs
How harmful is valproate to the fetus?

versus children whose mothers are healthy or have untreated epilepsy

- Major congenital malformations: 11%
  - 3x

- Poor neurodevelopmental outcomes:
  - Cognitive developmental delay: 7x
  - Autism spectrum disorder: 3x
  - Autism: 5x
  - Milder cognitive problems: Increased risk

New measures to avoid valproate exposure in pregnancy endorsed
Member State representatives agree new restrictions and pregnancy prevention programme
1. Pregnancy:

- Valproate should not be used in pregnant girls or women who have a mental illness

- *Use only allowed for* –

  pregnant girls or women with epilepsy who have not responded to other anti-epileptic drugs and would otherwise be at serious risk

2. Women or girls with mental illness and childbearing potential:

- Valproate should not be used unless other treatments are ineffective or not tolerated.

- Valproate may be initiated in this patient group *only* if the *pregnancy prevention programme* is followed.
Guidance on valproate prescribing

1. Tools and guidance on MHRA website

2. RCPsych position statement (2018): withdrawal of valproate and pharmacological alternatives

3. Capacity and contraception issues: joint guidance by several Royal Colleges and other bodies

1 https://www.gov.uk/guidance/valproate-use-by-women-and-girls#current-advice


Valproate Prescriptions in last 10 years
Women with childbearing potential – pregnancy women

(January 2010 – December 2019)

From:
Clinical Practice Research Datalink GOLD database.
https://www.gov.uk/guidance/valproate-use-by-women-and-girls#monitoring-impact
Carbamazepine

- Reported to increase congenital anomalies up to 2-fold\(^1\)

- ‘last line’ choice for bipolar disorder (BAP Guidelines, 2016)\(^2\)

- Do not offer to women who are pregnant or have childbearing potential (NICE 2014)\(^3\)

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Lamotrigine

- Does probably not cause fetal anomalies\(^1\)

- Meta-analysis\(^2\) found association with autism spectrum disorder but very small sample and wide confidence intervals

- Recent larger population register study found no association after controlling for confounding factors\(^3\)

Lamotrigine pharmacokinetics - perinatal period

- Majority of pregnant women have large increase in clearance
  - Minority have small increase
- If possible, monitor levels from preconception/ 1st trim until 3 weeks pn.  
  - Also monitor mood closely

Lithium – use in pregnancy

From:
The Health Improvement Network Primary Care Database¹

Prescriptions discontinued in 2/3 of women in early pregnancy

About 1/10,000 pregnant women are prescribed lithium beyond the 6th week

1. McCrea et al 2015. PLOS ONE | DOI:10.1371/journal.pone.0121024
How teratogenic is lithium?

1 Historical study - ‘Lithium baby register’ (N=225)¹

- Ebstein anomaly: 6 (2.7%) vs 1: 20,000 reported for general population
- Cardiovascular defects: 18 (8%) vs < 1% in general population
- Poor design - favouring reporting of problems

Recent reviews²:

- Original observations likely to be overestimate

² McKnight et al, Lancet. 2012 Feb 25;379(9817):721-8
European Ebstein study

- 15 congenital anomaly registers in European countries (covering 5.6 million births)
- 173 unexplained Ebstein cases – none exposed to lithium

Cohort study – Patorno et al 2017

N Engl J Med 376; 23

- Medicaid data
- 1.3 million pregnant women
- 663 children exposed to lithium
- 1st trimester
Results:

• No increase in non-cardiac malformations

• Heart defects 2.41 % (exposed) vs 1.15 % (controls) (adjusted risk ratio 1.65; CI 1.02–2.68)

• Similar difference when treated and untreated women with BD were compared

• Similar difference when lithium and lamotrigine were compared

• No Ebstein cases!
Relationship of cardiac anomalies with dose

- \( \leq 600 \text{ mg} \): 1.11 (0.46 to 2.64)
- 601-900 mg: 1.60 (0.67 to 3.80)
- >900 mg: 3.22 (1.47 to 7.02)

**Adjusted risk ratio**
Meta – analysis of six cohort studies\(^1\)

- 727 exposures in pregnancy (mostly in 1\(^{\text{st}}\) trimester)
- 21,397 women with mood disorders *but no lithium in pregnancy*

**Results:**

- Total major malformations higher in exposed group:
  \[7.4\% \text{ (CI 4.0–10.7) vs 4.3\% (CI 3.7–4.8)}\]
- **pooled aOR 1.71**, (CI 1.07–2.72)
- But no increased cardiac malformations
- Only looked at septal defects, Ebstein
- Could not take account of some confounders (eg substance and alcohol misuse, obesity, severity of illness)

Summary – teratogenicity

• The risk of Ebstein’s anomaly after lithium exposure has not been found to be increased since original study

• Whether very small risk difficult to exclude!

• There may be a small risk of other cardiac malformations after higher doses of lithium and a small risk of congenital malformations in general

• Associations may be due to residual confounding (severity of illness, type of bipolar disorder, substance and alcohol misuse etc)
Pregnancy outcomes and neonatal health

- Few systematic studies
- No increase in several adverse pregnancy outcomes (PTB, SGA, placental abruption) \(^1\)
- Case reports of neonates with side effects seen in adults
- 1 study - higher risk of neonatal readmission (aOR 1.62, 1.12-2.33)\(^2\)
- No deaths reported

Neurodevelopment

- Very limited data
- 3 studies (N = 98, 1 prospective, 2 retrospective)
- No suggestion of neurodevelopmental delays\(^3\)

Prescribing lithium in pregnancy

- Lithium is recommended as the initial long-term therapy for the prevention of bipolar episodes\(^1,2\)

- In a woman taking lithium and planning a pregnancy or in the 1\(^{st}\) trimester, a need to switch to an antipsychotic is now less compelling.

- Patient can stay on lithium if it is clear that she needs a mood stabilizer, there is evidence that she has responded to lithium and that the risk of relapse would be high if it was discontinued and replaced by an antipsychotic

- If the woman requires a second mood stabilizer in addition to an antipsychotic this should be lithium and not valproate or carbamazepine

PRESCRIBING LITHIUM IN PREGNANCY

Renal function
- increases until mid-pregnancy and then decreases again
- Lithium levels mirror these changes

Analysis of 1,101 Lithium serum levels (Wesseloo et al, 2017)

Measuring lithium levels in pregnancy

- NICE (2014)\textsuperscript{1} recommends:
  - 1 x / month up to week 36 of pregnancy
  - 1 x / week in month before expected delivery date

- Underdosing is now more of a problem in practice than overdosing\textsuperscript{2}

\textsuperscript{1}National Institute of Health and Care Excellence (2014) Clinical Practice Guideline 192
\textsuperscript{2}Wesseloo et al (2017), BJP 211: 31-36; DOI: 10.1192/bjp.bp.116.192799
Sub-therapeutic levels in pregnancy

Lithium level < 0.05 mmol/L

Preconception | 1st trimester | 2nd trimester | 3rd trimester | Postpartum

Measuring lithium levels in pregnancy

- Measuring creatinine as well each time
- Close liaison with midwife and obstetrician about changes in renal function
- Beware of ureter compression in late pregnancy, pre-eclampsia and any other causes of renal impairment
Managing lithium dose peripartum

During delivery

• Continue dose\(^1\)
• Measure level daily, 12 hours after each dose\(^2\) and adjust dose
• Monitor fluid balance and electrolytes\(^1\)

Postnatally

• Repeat blood samples (1\(^{st}\) postnatal day and at least once more in 1\(^{st}\) week)
• Check level twice also in 2\(^{nd}\) week\(^2\)

Anxiolytics and sleep-inducers

Benzodiazepines

- Probably not teratogenic\(^1,2,5\)
- Floppy babies, respiratory depression

Hypnotic benzodiazepine receptor agonists (Z – drugs)

- Not teratogenic\(^2,3\)
- Zolpidem: possibly some increased risk for preterm birth, small size of baby for gestational age, low birthweight – but effects are small (ORs1.5-1.7)\(^4\)

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Benzodiazepines and Z-Drugs

*Newer studies on neurodevelopmental outcomes*¹,²,³,⁴:

- Small increase of internalizing behaviour in one study
- No other major problems identified

Other drugs

Promazine

- Very little known about 1st trimester exposure\(^1\)

Promethazine

- More data but older studies with problems
- No safety issues reported

Pregabalin

- 1 population study\(^2\) and 1 National cohort study\(^3\) (N=477 and 1,671) found no association with malformations

Prescribing anxiolytics and sleep-inducers in pregnancy

Benzodiazepines and Z-drugs

• Only use short-term for severe anxiety or agitation
• Do not use zolpidem
• Monitor infant’s breathing

Pregabalin

• Avoid

Promazine, promethazine or quetiapine?

• Preferably avoid but difficult to replace
• Efficacy of quetiapine to anticipate in second half of pregnancy
Breastfeeding

2018¹:

‘exclusive breastfeeding for 6 months is the optimal way of feeding infants’

¹. https://www.who.int/nutrition/topics/exclusive_breastfeeding/en/
Psychotropics & breastfeeding

- All psychotropic drugs are transferred into breast milk
- Exposure of infant during breastfeeding is usually much less than during pregnancy
- Few data for most psychotropic drugs
Relative infant dose (RID)

| infant dose in mg /kg | maternal dose/ kg |

- < 10% ‘relatively safe’ (Bennett, 1996) ¹
- Most psycho-tropics are well below 10 %, but some exceptions

¹Bennett PN (1996) Use of monographs in drugs. In: Bennett PN (Editor), Drugs and Human Lactation (pp 67-74). Amsterdam: Elsevier Science Publishers
Psychotropics and breastfeeding$^{1,2,3}$

**Antipsychotics:**

- Very low transfer into breast milk except for amisulpiride, supiride, haloperidol and risperidone.
- Few side effects reported (case literature): sedation, slowing of development, and irritability, especially when other antipsychotic or sedative medication co-prescribed.
- Avoid clozapine (agranulocytosis, seizures).
- Aripiprazole reduces prolactin - cases of impaired milk production described.

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$^1$ Drugs and Lactation Database (LactMed) (2019); https://www.ncbi.nlm.nih.gov/books/NBK501153/
Mood stabilizers:

- Don’t offer lithium (high infant serum levels reported)$^{1,2}$
- Don’t offer valproate and carbamazepine$^1$
- Caution with lamotrigine: infant plasma can be high, monitor infant for breathing difficulty, skin rash, excessive drowsiness and poor sucking$^2$

Antidepressants$^1$:

- Most drugs: very low transfer into breast milk
- Exceptions are venlafaxine, fluoxetine and citalopram – but few side-effects reported
- Previous response is important in selecting antidepressant

$^1$ National Institute of Health and Care Excellence (2014) Clinical Practice Guideline 192
$^2$ Drugs and Lactation Database (LactMed) (2019); https://www.ncbi.nlm.nih.gov/books/NBK501153/
Anxiolytics and sleep inducers

- Benzodiazepines:
  Avoid long-acting agents – they tend to accumulate in infants
  Only use if essential
  Only short-term

- Promazine: no data

- Promethazine: probably not teratogenic, but may impair lactation

- Pregabalin: very limited data, RID < 10

- Zolpidem: very limited data, high RID, 1 case of infant drowsiness

- Zopiclone, zaleplon: low RID, but very limited data

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General advice to mother

• If she is significantly sedated by medication she should not breastfeed or only with supervision

• Monitor baby for side effects (sedation, muscle tone, EPSE, other side-effects)

• If in doubt ask advice from community midwife/health visitor/ GP