Perinatal Mental Health:
Prescribing Guidance
for Trust Prescribers and GPs

Version 4 – June 2018
(Now includes guidance on ADHD drugs and updated guidance on use of valproate in women of child-bearing potential).

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This updated guidance was approved by the Trust Drugs & Therapeutics Group in January & July 2018, and supersedes the 2015 version of the document.

If you require this document in an alternative format, ie, easy read, large text, audio, Braille or a community language please contact the Pharmacy Team on 01243 623349. (Text Relay calls welcome).
## 1. Summary of Medication Use

### Table of preferred (lower risk) medication in pregnancy:

<table>
<thead>
<tr>
<th>Category</th>
<th>Medication</th>
</tr>
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<tbody>
<tr>
<td>Antidepressants</td>
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<td></td>
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### Table of preferred (lower risk) medication in breast-feeding:

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</table>
2. Principles of Prescribing

Not treating mental health problems in pregnancy carries risks:
Symptoms of mental illness can result in missed scans and midwife
appointments, and risky behaviour.

There is good evidence\(^1,2\) that maternal anxiety and depression in pregnancy
result in childhood emotional and behavioural problems (independent of
postnatal factors that influence development of childhood mental ill health).
Trying to avoid treatment with psychotropics in pregnancy is not always in the
best interests of the patient or the foetus or the wider family. If women
relapse after stopping medication they can subsequently need more
medication at higher doses.

**NICE Clinical Guidelines: Antenatal and Postnatal Mental Health\(^3\):**
- When discussing medication in pregnancy, acknowledge that there is
  uncertainty surrounding risks.
- Explain the risks of treating versus not treating mental health conditions
  and the background risk of malformations in women without mental
disorder; this is between 2- 4 in 100.
- Discuss the risk of relapse. Consider when the last episode was, its
  severity and the response to treatment.
- Discuss the risks of stopping medicines suddenly. Consider high risk of
  relapse and risk of withdrawal symptoms.

Some general principles when prescribing in pregnancy:
- Data are often scarce and often rely on human case reports & pre-
clinical animal studies.
- Studies are often problematic due to confounders and results need to
  be treated with caution. Women on antidepressants and antipsychotics
  are more likely to drink, smoke, not attend antenatal care, have poor
  nutrition and be on other medication. These factors, and others, may
  affect maternal and neonatal outcomes.
- Need to balance with risks of treating against those of not treating.
- Generally use the lowest effective dose for shortest time period.
- Where possible, avoid newer drugs that have fewer data on use.
- Monotherapy is always preferable.
- Consider risks at different times, particularly the first trimester.
- Ensure adequate foetal or infant screening is performed or a foetal
  medicine referral is made if needed.
- **Clearly document all prescribing decisions.**
- Also consider those women who are **planning pregnancy**. If possible
  review and rationalise medication prior to actual pregnancy.
- Refer to local Perinatal Mental Health Service for specialist
  assessment and advice, particularly for women with a history of severe
  or complex mental health problems.
3. **Summary of Medication Use in Pregnancy**

It is preferable for a woman to take a medication during pregnancy and breastfeeding which works well for her rather than attempting to change to an alternative which may have a potentially better side-effect profile. The risks associated with a potential relapse or deterioration in mental state would usually outweigh those associated with possible adverse foetal outcomes.

It is generally inadvisable to stop a medication that a woman has required to achieve wellness or stability solely if she becomes pregnant. If there are concerns about her prescription, please contact your local Perinatal Mental Health team.

**Table of preferred (lower risk) medication:**

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# There is wide experience with some **first generation antipsychotics**, (chlorpromazine, haloperidol, trifluoperazine), although safety cannot be considered fully established. They are generally also avoided due to their less acceptable overall side-effect profile and should not be initiated during pregnancy (or breast-feeding) other than within specialist perinatal services.

### Sodium valproate and valproic acid are absolutely contraindicated in pregnancy. They are also contraindicated in women of child-bearing potential **without a clearly documented rationale**. Women taking this medication should be taking a reliable form of reversible contraception and should be informed of the need to inform their GP or prescriber prior to trying to conceive. **(See page 8 for further information).**
4. Antidepressants in Pregnancy

Antidepressants are generally well tolerated in pregnancy and breastfeeding by both women and their infants. Antenatal and postnatal depression are associated with adverse foetal, maternal and infant outcomes and should be treated. The risks associated with antidepressant treatment are often outweighed by those associated with illness.

Studies have shown evidence of some risks. These studies are prone to being subject to incompletely controlled confounders. Larger and better controlled studies tend to show a smaller increase in risks. The potential risks include:

- Small increased risk (1-2%) of birth defects, mainly cardiac. A recent meta-analysis showed that overall antidepressants do not appear to be associated with an increased risk of congenital malformations, but statistical significance was found for cardiovascular malformations. Given that the relative risks are marginal, they may be the result of uncontrolled confounders. Although the relative risks were statistically significant none reached clinically significant levels.
- Small increased risk of reduced intrauterine growth rate (IUGR), low birth weight (LBW) and low APGAR score.

**Do Antidepressants cause autism?**

A Swedish study of 600,000 children found those born to a mother with a history of maternal depression were at higher risk of developing an autistic spectrum disorder, particularly autism without intellectual disability. The association was strongest in those women on antidepressants antenatally, both SSRIs and other antidepressants.

A causal association with antidepressant use in pregnancy may explain 0.6% of ASD cases. However,

- Data could be confounded by indication for prescription
- Antidepressant use in pregnancy is an indicator of more severe depression and there is an association between severe depression and autism
- This study does not provide evidence to say we should stop treating moderate to severe depression in pregnancy with antidepressants

**SSRIs and Persistent Pulmonary Hypertension**

One study showed small increased risk of persistent pulmonary hypertension with SSRIs used after 20 weeks, but numbers were small: 6-12/1000, compared to 1-2/1000 in the general population. Subsequent large scale studies have failed to reproduce this finding. Overall risks are therefore considered to be smaller than this.

**Neonatal Withdrawal**

All antidepressants are associated with withdrawal in the neonate but it is usually mild and self-limiting. Withdrawal symptoms are slightly reduced with
fluoxetine due to its long half-life. Symptoms include sleeping problems, tremors, constant crying, suckling problems, and myoclonus. Symptomatic treatment is normally not required. If there are significant symptoms, then the neonate may need to remain in hospital for a short period of time, usually less than 48 hours.

**Paroxetine**
According to NICE, this is the only antidepressant absolutely contraindicated in pregnancy, due to its association with foetal heart defects.

**Venlafaxine**
Although venlafaxine is not recommended by NICE, perinatal psychiatrists and obstetricians use it frequently in treatment-resistant patients. However, blood pressure must be monitored more closely throughout the pregnancy.

### 5. Antipsychotics in Pregnancy

The United Kingdom Teratology Information Service currently recommends the use of **olanzapine and quetiapine** in pregnancy.

Previously there was more data informing the use of first-generation antipsychotics, such as haloperidol, but this is no longer the case. Recent evidence from a large population based Scandinavian cohort study provides high quality evidence on the safety of aripiprazole alongside quetiapine and olanzapine showing no increased rate of congenital abnormalities or cardiac abnormalities. This study did show that risperidone use may carry a 30% increased risk of cardiac abnormalities, so its use is not currently recommended as more study is needed.

**Second generation atypical antipsychotics** are associated with low folate levels so during pre-pregnancy counselling, the use of folic acid supplementation (eg. 5mg / day) should be considered / discussed.

**Olanzapine and quetiapine** are associated with weight gain and gestational diabetes so this needs to be monitored closely during pregnancy. Patients on olanzapine should have a GTT at 24-28 weeks even if they have no other risk factors for GDM.

NICE advises against prescribing **long-acting antipsychotic injections and anticholinergic drugs**.

**Clozapine** can be used in pregnancy if necessary but this must be under the supervision of secondary care services.

Neonatal toxicity & withdrawal have been reported but again this is very mild and self-limiting.
6. Mood Stabilisers in Pregnancy

Olanzapine, quetiapine and aripiprazole are considered safer options than more traditional mood stabilisers.

Lithium:
Should be avoided if possible, especially in the first trimester and, where possible, prescribing stopped before conception. If it is continued, this must be under secondary care supervision. There is a possible increase in the risk of congenital malformations. Ebstein’s anomaly was previously considered to be 20 times more likely if a foetus was exposed to lithium but this has not been replicated by further studies.

Cessation of lithium should be done gradually over at least four weeks. If the woman is not well, she can be switched to an antipsychotic or lithium restarted in the second trimester if she is not planning to breastfeed.

If lithium is continued, serum levels must be checked every four weeks aiming for the lower end of the therapeutic range.

Higher doses may be needed towards the end of pregnancy. Serum levels must be checked every week from week 36 and then checked within 24 hours after birth. Birth should take place within hospital.

Sodium Valproate:
This drug is absolutely contraindicated in pregnancy and should also not be prescribed to any women of child-bearing potential unless absolutely necessary and the conditions of the Pregnancy Prevention Programme are met. (See below). If prescribed, the rationale for this must be clearly documented and the patient must be made fully aware of the risk.

There is a high risk of neural tube defects, (risks raised from 6/10,000 to 100-200/10,000). It can also affect intellectual development of children in up to 30% of cases - (valproate syndrome).


Further to this, the link below is to the MHRA Drug Safety Alert (May 2018), which provides links to online materials to help practitioners ensure that women and girls taking valproate medicines meet the requirements of the new Pregnancy Prevention Programme. In addition, it provides links to e-copies of the Patient Card, Patient Guide, a Guide for Healthcare Professionals and the Risk Acknowledgement Form. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/710841/DSU-May-PDF.pdf
Carbamazepine:
NICE recommend that this drug is not routinely prescribed during pregnancy due to the risk of neural tube defects; (risk raised from 6/10,000 to 20-50/10,000). It has also been linked to other major malformations, gastrointestinal tract problems and cardiac abnormalities.

Lamotrigine:
NICE recommend that this drug is not routinely prescribed during pregnancy citing a risk of oral cleft of around 9/1000. However, a recent study suggests that the risk is lower or not present\(^9\). Data are limited at present but the available evidence does not suggest it is a major teratogen.

Folic Acid Deficiency:
This is known to occur in pregnancy and may contribute to birth defects. Antiepileptic drugs, (eg. valproate, carbamazepine and lamotrigine), are reported to aggravate this deficiency and folic acid supplements are therefore highly recommended before and during pregnancy. However, note that for valproate, in particular, evidence does not suggest that such supplementation prevents birth defects or malformations.

7. Benzodiazepines in pregnancy
NICE recommends that these drugs only be used short-term, if considered necessary for extreme anxiety and agitation.

They may be associated with cleft palate and other malformations. Maternal use of a benzodiazepine during pregnancy is also associated with an increased risk of preterm delivery. Floppy baby syndrome in neonate and neonatal withdrawal are also possible.

8. Other hypnotics in pregnancy
NICE suggest the use of low dose chlorpromazine or amitriptyline in response to serious and chronic problems.

However, many perinatal psychiatrists prefer to use a sedating antihistamine, e.g. promethazine.

Z-drugs are not recommended by NICE but zopiclone is used by some perinatal psychiatrists for short-term use.

9. ADHD medications in pregnancy
There is limited evidence regarding the use of methylphenidate, atomoxetine, lisdexamfetamine and dexamfetamine in pregnancy and breastfeeding. Guanfacine has shown toxicity in animal studies and should not be used.
Methylphenidate may be associated with an increased risk of cardiac malformations based upon one study but other research has not confirmed this. Both untreated ADHD and methylphenidate use are associated with an increased risk of miscarriage. Dexamphetamine and atomoxetine do not appear to be associated with congenital malformations. All may be associated with a withdrawal syndrome although this does not appear to be severe. There is no evidence of methylphenidate or dexamphetamine causing problems during breastfeeding. There is very limited evidence around atomoxetine in breastfeeding but there are no reports of harm. As with other medications, the risks and benefits associated with taking the medication or not must be balanced; remembering that leaving people untreated can be associated with significant risks in some cases.

10. Prescribing in Breast-feeding

NICE Clinical Guidelines advise that breast-feeding should not be discouraged. Rather, wherever possible, the safest treatment available should be used so that breast-feeding can still take place.

Table of preferred (lower risk) medication in breast-feeding:

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It should be noted that for many drugs there are very little data on levels in breast milk and safety in breast-feeding and therefore recommendations in reference texts are often based on just a small number of case reports.

Similarly, there is no clear evidence or information for the vast majority of drugs on the timing of feeds with regard to timing of doses, or on whether milk at certain times of day should be discarded.

Manufacturers of atomoxetine, methylphenidate, dexamphetamine, lisdexamfetamine and guanfacine, all advise avoidance of breast-feeding due to scarcity of safety data from human studies.
Based on various information sources, the following drugs (in particular) should be avoided or if unavoidable used with caution:

<table>
<thead>
<tr>
<th>Category</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antidepressants</td>
<td>Clomipramine, Dosulepin, <strong>Doxepin - avoid</strong> Duloxetine, MAOIs, Reboxetine, Venlafaxine</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td><strong>Clozapine – Avoid due to risk of neonatal agranulocytosis</strong> Pimozide</td>
</tr>
<tr>
<td>Mood stabilisers</td>
<td><strong>Lithium – avoid</strong> (very high levels possible in breast milk and in infant serum), <strong>Lamotrigine – avoid</strong> - Risk of serious dermatological problems in the infant – eg. Stevens-Johnson syndrome.</td>
</tr>
<tr>
<td>Hypnotics</td>
<td><strong>Zopiclone – avoid</strong> (high levels in breast milk) Benzodiazepines – avoid long-acting or in high dose</td>
</tr>
</tbody>
</table>

11. Information Sources on Perinatal Prescribing

- iPhone app: Lactmed – free to download and available online at: [https://toxnet.nlm.nih.gov/pda/lactmed.htm](https://toxnet.nlm.nih.gov/pda/lactmed.htm)
- Summaries of Product Characteristics (or contact the individual drug manufacturer): [http://www.medicines.org.uk/emc/](http://www.medicines.org.uk/emc/)
- The Maudsley Prescribing Guidelines – Book or app, both around £50
- Psychotropic Drug Directory – Stephen Bazire

12. Contact details for Sussex Perinatal Mental Health Teams

**Referral email:** spnt.perinatalreferrals@nhs.net

**Brighton and Hove Perinatal Mental Health Team**
East Brighton Community Mental Health Centre
Elm Grove
Brighton
East Sussex
BN2 3EW
Tel: 0300 304 0089
Coastal West Sussex Perinatal Mental Health Team
Swandeau
Worthing
West Sussex
BN13 3EP
Tel: 0300 304 0214

North West Sussex and East Surrey Perinatal Mental Health Team
New Park House
North Street
Horsham
West Sussex
RH12 1RJ
Tel: 0300 304 0021

East Sussex Perinatal Mental Health Team
Woodside
The Drive,
Hellingley
Hailsham
East Sussex
BN27 4ER
Tel: 01323 446042

13. References


