

Perinatal Mental Health: Prescribing Guidance for Trust Prescribers and GPs

(Version 3 – January 2018)

Principal Authors:

Dr Jenny Cooke – Consultant Psychiatrist,
Brighton & Hove Perinatal Mental Health Service

Dr Michael Rutherford – Consultant Psychiatrist
Coastal West Sussex Perinatal Mental Health Service

Supported by:

Jed Hewitt – Chief Pharmacist, Governance & Professional Practice

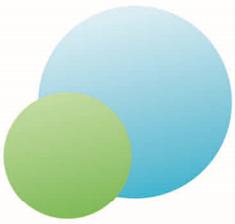
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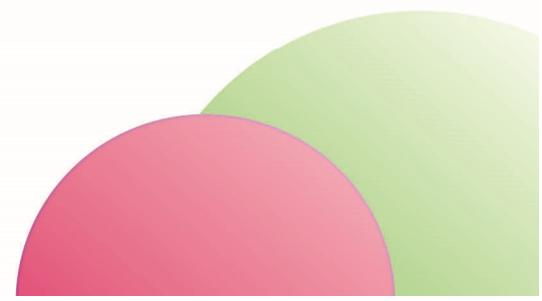
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(Text Relay calls welcome).

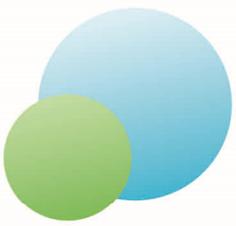




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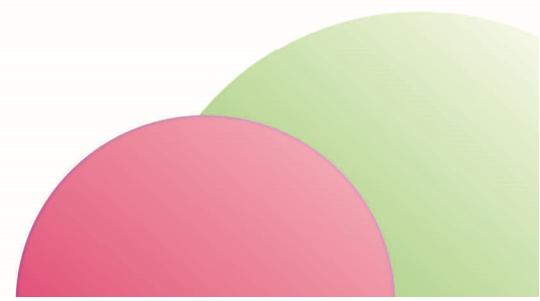
1. Summary of Medication Use

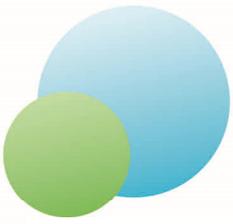
Table of preferred (lower risk) medication in pregnancy:

Antidepressants	Sertraline Citalopram Escitalopram Fluoxetine
Antipsychotics	Olanzapine Quetiapine Aripiprazole
Mood Stabilisers	Olanzapine Quetiapine Aripiprazole
Hypnotics	Promethazine

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

Antidepressants	Sertraline (first-line choice) Citalopram
Antipsychotics	Olanzapine Quetiapine
Mood Stabilisers	Olanzapine Quetiapine
Hypnotics	Promethazine





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.

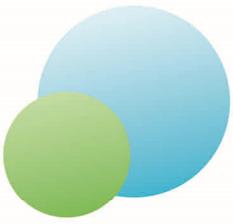
NICE Clinical Guidelines: Antenatal and Postnatal Mental Health³:

- 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.

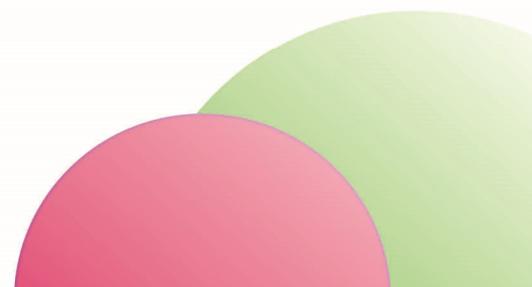
It is generally inadvisable to stop a medication that a woman has required to achieve wellness or stability solely if she becomes pregnant. If there are concerns about her prescription, please contact your local Perinatal Mental Health team.

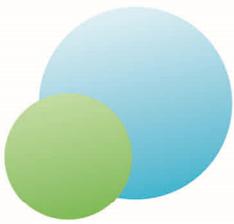
Table of preferred (lower risk) medication:

Antidepressants	Sertraline Citalopram Escitalopram Fluoxetine
Antipsychotics #	Olanzapine Quetiapine Aripiprazole
Mood Stabilisers ##	Olanzapine Quetiapine Aripiprazole
Hypnotics	Promethazine

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 specifically contraindicated in women of childbearing age 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-analysis³ 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 study⁴ 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,

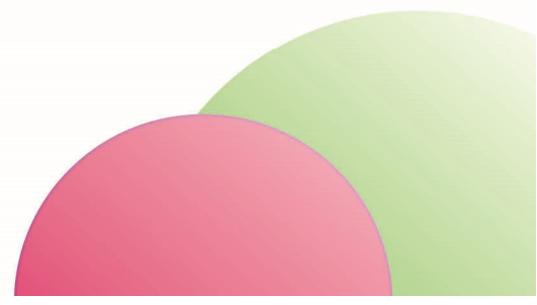
- Data could be confounded by indication for prescription
- Antidepressant use in pregnancy is an indicator of more severe depression and there is an association between severe depression and autism
- This study does not provide evidence to say we should stop treating moderate to severe depression in 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 finding⁵. 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.

3. Antipsychotics in Pregnancy

The United Kingdom Teratology Information Service currently recommends the use of **olanzapine and quetiapine** in pregnancy⁶.

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 study⁷ 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.

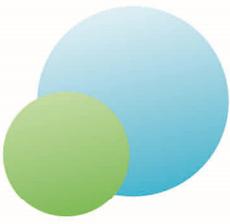
Olanzapine and quetiapine are associated with weight gain and gestational diabetes so this needs to be monitored closely during pregnancy. Patients on olanzapine should have a GTT at 24-28 weeks even if they have no other risk factors for GDM.

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.





4. 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 Valproate⁸:

This drug is absolutely contraindicated in pregnancy and should also not be prescribed to any women of child-bearing potential unless absolutely necessary. If prescribed, the rationale for this must be clearly documented and the patient must be 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).

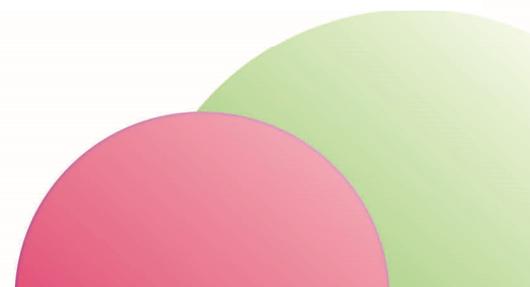
<https://www.gov.uk/drug-safety-update/valproate-and-developmental-disorders-new-alert-asking-for-patient-review-and-further-consideration-of-risk-minimisation-measures>

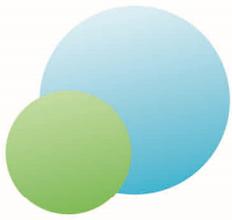
Carbamazepine:

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 present⁹. 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.

5. 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.

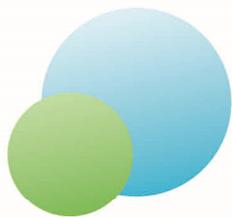
6. Other hypnotics in pregnancy

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. Prescribing in Breast-feeding

NICE Clinical Guidelines³ 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:

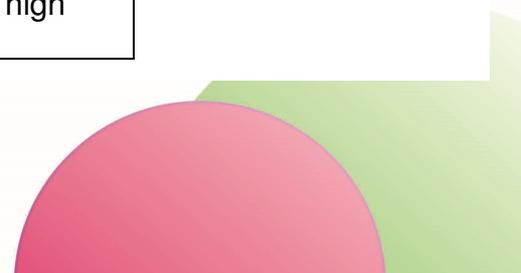
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Antipsychotics # (See note on page 5).	Olanzapine Quetiapine
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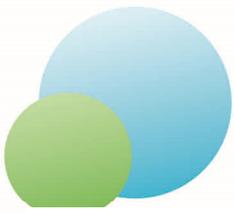
It should be noted that for many drugs there are very little data on levels in breast milk and safety in breast-feeding and therefore recommendations in reference texts are often based on just a small number of case reports.

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.

Based on various information sources, the following drugs (in particular) should be avoided or if unavoidable used with caution:

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





10. Information Sources on Perinatal Prescribing

- UK Teratology Information Service: 08448920909: <http://www.uktis.org/>
- iPhone app: Lactmed – free to download and available online at: <https://toxnet.nlm.nih.gov/pda/lactmed.htm>
- Summaries of Product Characteristics (or contact the individual drug manufacturer): <http://www.medicines.org.uk/emc/>
- The Maudsley Prescribing Guidelines – Book or app, both around £50
- Psychotropic Drug Directory – Stephen Bazire

11. 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 0097

Coastal West Sussex Perinatal Mental Health Team

Swandean
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 0213

East Sussex Perinatal Mental Health Team

Woodside
The Drive
Hellingly
Hailsham
East Sussex
BN27 4ER
Tel: 0300 304 0212

Specialist Perinatal Mental
Health Service (SPMHS)





12. References

1. NICE. Antenatal and postnatal mental health: clinical management and service guidance - Clinical guideline [CG192]. Updated August 2017. Available from: <https://www.nice.org.uk/guidance/cg192>
2. McAllister-Williams RH et al. British Association for Psychopharmacology consensus guidance on the use of psychotropic medication preconception, in pregnancy and postpartum 2017. *Journal of Psychopharmacology*. 2017;31(5):1-34.
3. Grigoriadis et al. The impact of maternal depression during pregnancy on perinatal outcomes: a systematic review and meta-analysis. *Journal of Clinical Psychiatry*. 2013;74(4):293-308.
4. Raj et al. Parental depression, maternal antidepressant use during pregnancy, and risk of autism spectrum disorders: population based case-control study. *BMJ*. 2013;346:f2059.
5. Huybrechts et al. Antidepressant Use Late in Pregnancy and Risk of Persistent Pulmonary Hypertension of the Newborn. *JAMA Psychiatry*. 2015; 313(21):2142-2151.
6. UK Teratology Information Service. 6. UK Teratology Information Service [Internet]. UK:UKTIS [updated 2017.12.08; cited 2018.01.02]. Available from: <http://www.uktis.org/>.
7. Huybrechts et al. Antipsychotic Use in Pregnancy and the Risk for Congenital Malformations. *JAMA Psychiatry*. 2016;73(9):938-46.
8. Valproate and developmental disorders: new alert asking for patient review and further consideration of risk minimisation measures. (April 2017). <https://www.gov.uk/drug-safety-update/valproate-and-developmental-disorders-new-alert-asking-for-patient-review-and-further-consideration-of-risk-minimisation-measures>
9. Dolk H et al. 2016. Lamotrigine use in pregnancy and risk of orofacial cleft and other congenital anomalies. *Neurology*;86(18):1716-1725.

