

Perinatal Mental Health: Prescribing Guidance for Trust Prescribers and GPs

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the Pharmacy Team on 01243 623349.
(Text Relay calls welcome).

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1. Summary of Medication Use

Table of preferred (lower risk) medication in pregnancy:

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

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

Antidepressants	Sertraline (first-line choice) Mirtazapine
Antipsychotics	Olanzapine Quetiapine
Mood Stabilisers	Olanzapine Quetiapine
Hypnotics and sedatives	Promethazine Lorazepam

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 to 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.
- 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 that 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 (see section 13)

Table of preferred (lower risk) medication:

Antidepressants	Sertraline Citalopram 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.

Do not offer valproate to women of childbearing potential for long-term treatment or to treat an acute episode. If no effective alternative to valproate can be identified, the prescriber needs to ensure that the standards of 'Pregnancy Prevention Programme' are met, including:

- Discussion of risks associated with prescribing of valproate in pregnancy
- Provision of written Pregnancy Prevention Programme material
- Completion of valproate risk acknowledgement form
- Ensure highly effective contraception if applicable.

(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 both 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 antenatal depression and autism, as well as other adverse outcomes.
- This study does not provide evidence to say we should stop treating moderate to severe depression in pregnancy with antidepressants.

Toxbase currently states that data regarding risk of autism following in utero exposure to SSRIs are conflicting and potentially confounded. Further studies are required before definitive conclusions can be provided.

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: 3-4/1000, 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

Paroxetine is generally not preferred in pregnancy as it appears to be associated with a higher risk of congenital abnormalities.

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 suggests **olanzapine and quetiapine** as reasonable to use 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 (e.g. 5mg / day) should be considered / discussed. This may be partially due to pre-existing obesity.

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 clinicians to not offer depot antipsychotics to a woman who is planning a pregnancy, pregnant or considering breastfeeding, unless she is responding well to a depot and has a previous history of non-adherence with oral medication.

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 Valproate⁸:

This drug is absolutely contraindicated in pregnancy and should also not be prescribed to any female of child-bearing potential unless absolutely necessary and the conditions of the Pregnancy Prevent Programme are met. If prescribed, the rationale for this must be clearly documented and the patient (and if appropriate the parents) 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).

The MHRA has produced various documents intended to support healthcare professionals and patients around valproate prescribing. These include: a patient guide, a guide for healthcare professionals, a risk acknowledge form and a patient card. These documents are available online at:

<https://www.gov.uk/guidance/valproate-use-by-women-and-girls#history>

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, (e.g. 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, but the evidence around this not as strong as previously thought. 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 and sedatives in pregnancy

NICE suggest the use of promethazine 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 and dexamphetamine in pregnancy and breastfeeding.

Methylphenidate may be associated with an increased risk of cardiac malformations based upon one study but other research has not confirmed this¹⁰. Both untreated ADHD and methylphenidate use are associated with an increased risk of miscarriage. Dexamphetamine, lisdexamphetamine 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, lisdexamphetamine 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.

There is no enough evidence around the safety of guanfacine in pregnancy and breastfeeding and other agents may be preferred as a consequence.

10. Medications for substance misuse

Most recreational drugs have adverse effects. Patients who are dependent upon alcohol, opiates, stimulants or other illicit drugs should be referred to local substance misuse services for specialist care.

The use of recreational drugs, including tobacco, alcohol, opiates and stimulants are associated with numerous adverse foetal and maternal outcomes when used during pregnancy. Ideally they should be discontinued prior to pregnancy, but if not, their use should be limited and ideally stopped.

Nicotine replacement therapy is not associated with adverse maternal or foetal outcomes and is effective in reducing tobacco use. There is limited data for the use of bupropion and varenicline.

Alcohol dependent patients can receive detoxification, but this should be in an inpatient setting. Chlordiazepoxide and diazepam are usually the medications of choice in this circumstance. There is insufficient data to recommend acamprosate, naltrexone or nalmefene.

Methadone and buprenorphine are both associated with improved foetal and maternal outcomes in opiate-dependent patients, with buprenorphine possibly resulting in better infant weights and less premature birth². Both reduce the incidence of severity of the neonatal abstinence syndrome². Management of opiate dependency in pregnancy should be via a specialist substance misuse service ideally with input from neonatology and obstetrics.

There is no evidence of pharmacotherapy in stimulant dependent and patients should be offered a psychosocial package of care.

11. 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. NICE states that clinicians should take care with any sedating medication, especially in the postnatal period, since excessive sedation can hinder baby care and breastfeeding. Although sedation can often resolve over a short period after starting a medication, alternative options may need to be considered. Women should be advised against co-sleeping with their babies.

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

Antidepressants	Sertraline (first-line choice) Mirtazapine
Antipsychotics # (See note on page 5).	Olanzapine Quetiapine
Mood Stabilisers	Olanzapine Quetiapine
Hypnotics and sedatives	Promethazine Lorazepam

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).
Hypnotics and sedatives	Benzodiazepines – avoid long-acting or in high dose

12. 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

13. 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

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 0021

East Sussex Perinatal Mental Health Team

Woodside
 The Drive,
 Hellingly
 Hailsham
 East Sussex
 BN27 4ER
 Tel: 01323 446042

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