Drug choice in pregnancy

A ‘normal’ outcome to pregnancy can never be guaranteed. The spontaneous abortion rate in confirmed early pregnancy is 10–20% and the risk of spontaneous major malformation is 2–3% (approximately 1 in 40 pregnancies). Lifestyle factors have an important influence on pregnancy outcome. It is well established that smoking cigarettes, eating a poor diet and drinking alcohol during pregnancy can have adverse consequences for the foetus. More recent data suggest that moderate maternal caffeine consumption is associated with low birth weight, and that pre-pregnancy obesity increases the risk of neural tube defects; (obese women seem to require higher doses of folate supplementation than women who have a BMI in the healthy range).

In addition, psychiatric illness during pregnancy is an independent risk factor for congenital malformations and perinatal mortality. Affective illness increases the risk of pre-term delivery.

Drugs account for a very small proportion of abnormalities (approximately 5% of the total). Potential risks of drugs include major malformation (first-trimester exposure), neonatal toxicity (third-trimester exposure), longer-term neurobehavioural effects and increased risk of physical health problems in adult life.

The safety of psychotropics in pregnancy cannot be clearly established because robust, prospective trials are obviously unethical. Individual decisions on psychotropic use in pregnancy are therefore based, at best on database studies that have many limitations including failure to control for the effects of illness and other medication, prospective data from teratology information centres and published case reports which are known to be biased towards adverse outcomes. At worst there may be no human data at all, only animal data from early preclinical studies. With new drugs early reports of adverse outcomes may or may not be replicated and a ‘best guess’ assessment must be made of the risks and benefits associated with withdrawal or continuation of drug treatment. Even with established drugs, data related to long-term outcomes are rare. Pregnancy does not protect against mental illness and may even elevate overall risk. The patient’s view of risks and benefits will have paramount importance. This section provides a brief summary of the relevant issues and evidence to date.

### General principles of prescribing in pregnancy

<table>
<thead>
<tr>
<th>In all women of child bearing potential</th>
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<tbody>
<tr>
<td>▪ Always discuss the possibility of pregnancy – many pregnancies are unplanned</td>
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<tr>
<td>▪ Try to avoid using drugs that are contra-indicated during pregnancy in women of reproductive age, (especially valproate and carbamazepine). If these drugs are prescribed, women should be made fully aware of their teratogenic properties even if not planning pregnancy. Consider prescribing folate</td>
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<tr>
<td>If mental illness is newly diagnosed in a pregnant woman</td>
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<tr>
<td>▪ Try to avoid all drugs in the first trimester (when major organs are being formed) unless benefits outweigh risks</td>
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<tr>
<td>▪ If non-drug treatments are not effective/appropriate, use an established drug at the lowest effective dose</td>
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<tr>
<td>If a woman taking psychotropic drugs is planning a pregnancy</td>
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<tr>
<td>▪ Consideration should be given to discontinuing treatment if the woman is well and at low risk of relapse</td>
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<tr>
<td>▪ Discontinuation of treatment for women with SMI and at a high risk of relapse is unwise, but consideration should be given to switching to a low risk drug. Be aware that switching drugs may increase the risk of relapse</td>
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<tr>
<td>If a woman taking psychotropic medication discovers that she is pregnant</td>
</tr>
<tr>
<td>▪ Abrupt discontinuation of treatment post-conception for women with SMI and at a high risk of relapse is unwise; relapse may ultimately be more harmful to the mother and child than continued, effective drug therapy</td>
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<tr>
<td>▪ Consider remaining with current (effective) medication rather than switching, to minimise the number of drugs to which the foetus is exposed</td>
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<tr>
<td>If the patient smokes (smoking is more common in pregnant women with psychiatric illness)</td>
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<tr>
<td>▪ Always encourage switching to nicotine replacement therapy – smoking has numerous adverse outcomes, NRT does not</td>
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<tr>
<td>In all pregnant women</td>
</tr>
<tr>
<td>▪ Ensure that the parents are as involved as possible in all decisions</td>
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<tr>
<td>▪ Use the lowest effective dose</td>
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<tr>
<td>▪ Use the drug with the lowest known risk to mother and foetus</td>
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<tr>
<td>▪ Prescribe as few drugs as possible both simultaneously and in sequence</td>
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<tr>
<td>▪ Be prepared to adjust doses as pregnancy progresses and drug handling is altered. Dose increases are frequently required in the 3rd trimester when blood volume expands by around 30%. Plasma level monitoring is helpful, where available. Note that hepatic enzyme activity changes markedly during pregnancy; CYP2D6 activity is increased by almost 50% by the end of pregnancy while the activity of CYP1A2 is reduced by up to 70%</td>
</tr>
<tr>
<td>▪ Consider referral to specialist perinatal services</td>
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<tr>
<td>▪ Ensure adequate foetal screening</td>
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<tr>
<td>▪ Be aware of potential problems with individual drugs around the time of delivery</td>
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<tr>
<td>▪ Inform the obstetric team of psychotropic use and possible complications</td>
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<tr>
<td>▪ Monitor the neonate for withdrawal effects after birth</td>
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<tr>
<td>▪ Document all decisions</td>
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</table>
What to include in discussions with pregnant women

Discussions should include:

- the woman’s ability to cope with untreated illness/sub-threshold symptoms
- the potential impact of an untreated mental disorder on the fetus or infant
- the risks from stopping medication abruptly
- severity of previous episodes, response to treatment and the woman’s preference
- the background risk of foetal malformations for pregnant women without a mental disorder
- the increased risk of harm associated with drug treatments during pregnancy and the postnatal period, including the risk in overdose (and acknowledge uncertainty surrounding risks)
- the possibility that stopping a drug with known teratogenic risk after pregnancy is confirmed may not remove the risk of malformations

Where possible, written material should be provided to explain the risks (preferably individualised). Absolute and relative risks should be discussed. Risks should be described using natural frequencies rather than percentages (for example, 1 in 10 rather than 10%) and common denominators (for example, 1 in 100 and 25 in 100, rather than 1 in 100 and 1 in 4)

Psychosis during pregnancy and postpartum

- Pregnancy does not protect against relapse
- Psychiatric illness during pregnancy predicts post-partum psychosis
- The risk of perinatal psychosis is 0.1–0.25% in the general population, but is about 50% in women with a history of bipolar disorder
- During the month after childbirth there is a 20-fold increase (to 30-50%) in the relative risk of psychosis
- The risk of recurrent post-partum psychosis is 50–90%
- The mental health of the mother in the perinatal period influences foetal well-being, obstetric outcome and child development

The risks of not treating psychosis include:

- harm to the mother through poor self-care or judgement, lack of obstetric care or impulsive acts
- harm to the foetus or neonate (ranging from neglect to infanticide)

It has long been established that people with schizophrenia are more likely to have minor physical anomalies than the general population. Some of these anomalies may be apparent at birth, while others are more subtle and may not be obvious until later in life. This background risk complicates assessment of the effects of antipsychotic drugs. (Psychiatric illness itself during pregnancy is an independent risk factor for congenital malformations and perinatal mortality).

Treatment with antipsychotics

Older, first generation antipsychotics are generally considered to have minimal risk of teratogenicity, although data are less than convincing, as might be expected.

- Most data originate from studies that included primarily women with hyperemesis gravidarum (a condition associated with an increased risk of congenital malformations) treated with low doses of phenothiazines. The modest increase in risk identified in some of these studies, along with no clear clustering of congenital abnormalities suggest that the condition being treated may be responsible rather than drug treatment
- There may be an association between haloperidol and limb defects, but if real, the risk is likely to be extremely low
- Neonatal dyskinesia has been reported with FGAs
- Neonatal jaundice has been reported with phenothiazines

It remains uncertain whether FGAs are entirely without risk to the foetus or to later development. However, this continued uncertainty and the wide use of these drugs over several decades suggest that any risk is small – an assumption borne out by most studies.

Data relating to second generation antipsychotics are growing.

- The extent of placental passage is highest for olanzapine followed by risperidone followed by quetiapine
- There are most data for olanzapine which has been associated with both lower birth weight and increased risk of intensive care admission, and with macrosomia; the last of these is consistent with the reported increase in the risk of gestational diabetes. Although olanzapine seems to be relatively safe with respect to congenital malformations, it has been associated with a range of problems including hip dysplasia, meningocele, ankyloblepharon, and neural tube defects, (an effect that could be related to pre-pregnancy obesity rather than drug exposure). Importantly there is no clustering of congenital malformations
- Limited data suggest that neither risperidone nor quetiapine are major teratogens in humans. There are virtually no published data relating to other SGAs
- The use of clozapine appears to present no increased risk of malformation, although gestational diabetes and neonatal seizures may be more likely to occur. There is a single case report of maternal overdose resulting in foetal death, and there are theoretical concerns about the risk of agranulocytosis in the foetus/neonate. NICE recommends that pregnant women should be switched from clozapine to another antipsychotic. However, for almost all women who are prescribed clozapine, a switch to a different antipsychotic will result in relapse. On the balance of evidence available, clozapine should usually be continued.

Overall, these data do not allow an assessment of relative risks associated with different agents and certainly do not confirm absolutely the safety of any particular drug. At least one study has suggested a small increased risk of malformation and caesarean section in people receiving antipsychotics. Older drugs may still be preferred in pregnancy, but, considering data available on some newer drugs, it may not now always be appropriate always to switch to these first generation drugs, should continued treatment be necessary. As with other drugs, decisions must be based on the latest available information and an individualised assessment of probable risks and benefits. If possible, specialist advice should be sought, and primary reference sources consulted.
Depression during pregnancy and postpartum\textsuperscript{29,30} (B,C)

- Approximately 10% of pregnant women develop a depressive illness and a further 16% a self-limiting depressive reaction. Much postpartum depression begins before birth.
- Risk may be at least partially genetically determined.
- There is a significant increase in new psychiatric episodes in the first 3 months after delivery. At least 80% are mood disorders, primarily depression.
- Women who have had a previous episode of depressive illness (postpartum or not) are at higher risk of further episodes during pregnancy and post-partum. The risk is highest in women with bipolar illness.
- It is unclear if depression increases the risk of spontaneous abortion, having a low birth weight or small for gestational age baby, or of pre-term delivery\textsuperscript{(D)}.

The risks of not treating depression include:

- harm to the mother through poor self-care, lack of obstetric care or self-harm.
- harm to the foetus or neonate (ranging from neglect to infanticide).

Treatment with antidepressants

The use of antidepressants during pregnancy is common; in the Netherlands, up to 2% of women are prescribed antidepressants at some point during their pregnancy\textsuperscript{36,37}, and in the US around 10% of women are prescribed antidepressants at some point during their pregnancy\textsuperscript{38,39,40}. The majority of prescriptions are for SSRIs. \textbf{Relapse rates are high} in those with a history of depression who discontinue medication. One study found that 68% of women who were well on antidepressant treatment and stopped during pregnancy relapsed, compared with 26% who continued antidepressants\textsuperscript{41}. Some data suggest that antidepressants may increase the risk of spontaneous abortion (but note that confounding factors were not controlled for)\textsuperscript{(D,E)}.

Antidepressants may also increase the risk of pre-term delivery, respiratory distress in the neonate, a low APGAR score at birth and admission to a special care baby unit\textsuperscript{(D,G,H,I)}. Some centres used mixed (breast/bottle) feeding to minimise withdrawal. With SGAs, discontinuation may not be necessary or desirable.

SSRIs

- Sertraline appears to result in the least placental exposure\textsuperscript{42}.
- SSRIs appear not to be major teratogens\textsuperscript{35,36}, with most data supporting the safety of fluoxetine\textsuperscript{43,44,45}. Note though that one study revealed a slight overall increase in rate of malformation with SSRIs\textsuperscript{46}. Database and case control studies have reported an association between SSRIs and anencephaly, craniosynostosis, omphalocele, and persistent pulmonary hypertension of the newborn\textsuperscript{47,48}. These associations have not been replicated.
- Paroxetine has been specifically associated with cardiac malformations\textsuperscript{49} particularly after high dose (> 25mg/day), first trimester exposure\textsuperscript{50}. However some studies have failed to replicate this finding for paroxetine\textsuperscript{51,52}, and have implicated other SSRIs\textsuperscript{53-55}. Other studies have found no association between any SSRI and an increased risk of cardiac septal defects\textsuperscript{56}.
- SSRIs have also been associated with decreased gestational age (mean 1 week), spontaneous abortion\textsuperscript{57} and decrease birth weight (mean 175 g)\textsuperscript{40,44-47,49,57}. The longer the duration of in-utero exposure, the greater the chance of low birth weight and respiratory distress\textsuperscript{56}. Three groups of symptoms are seen in neonates exposed to antidepressants in late pregnancy; those associated with serotonin toxicity, those associated with antidepressant discontinuation symptoms and those related to early birth\textsuperscript{58}. Third-trimester exposure to sertraline has been associated with reduced early APGAR scores\textsuperscript{59}. Third-trimester use of paroxetine may give...
rise to neonatal complications, presumably related to abrupt withdrawal. Other SSRIs have similar, possibly less severe effects. Data relating to neurodevelopmental outcome of foetal exposure to SSRIs suggest that these drugs are safe, although data are less than conclusive. Depression itself may have more obvious adverse effects on development. Although associated with an increased risk of bleeding overall, SSRIs do not seem to confer a disproportionate risk of postpartum haemorrhage.

Other antidepressants
- Rather more scarce data suggest the absence of teratogenic potential with moclobemide, reboxetine and venlafaxine (although neonatal withdrawal may occur). Second trimester exposure to venlafaxine has been associated with babies being born small for gestational age (f). None of these drugs can be specifically recommended. Similarly, trazodone, bupropion (amfebutamone) and mirtazapine cannot be recommended because there are few data supporting their safety. Recent data suggest that both bupropion and mirtazapine are not associated with malformations but, like SSRIs, may be linked to an increased rate of spontaneous abortion. Bupropion exposure in-utero has been associated with an increased risk of ADHD in young children. MAOIs should be avoided in pregnancy because of a suspected increased risk of congenital malformation and because of the risk of hypertensive crisis. There is no evidence to suggest that ECT causes harm to either the mother or foetus during pregnancy although general anaesthesia is of course not without risks. In resistant depression, NICE recommend that ECT is used before/instead of drug combinations.
- Omega-3 fatty acids may also be a treatment option although efficacy and safety data are scant.

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<thead>
<tr>
<th>Recommendations – depression in pregnancy</th>
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<tbody>
<tr>
<td>Patients who are already receiving antidepressants and are at high risk of relapse are best maintained on antidepressants during and after pregnancy</td>
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<tr>
<td>Those who develop a moderate or severe depressive illness during pregnancy should be treated with antidepressant drugs</td>
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<tr>
<td>There is most experience with amitriptyline, imipramine (constipation and sedation can be a problem with both; withdrawal symptoms may occur) and fluoxetine (increased chance of earlier delivery and reduced birth weight). If the patient is established on another antidepressant, always obtain the most up-to-date advice. Experience with other drugs is growing and a change in treatment may not be necessary or wise. Paroxetine may be less safe than other SSRIs</td>
</tr>
<tr>
<td>The neonate may experience discontinuation symptoms such as agitation and irritability, or even convulsions (with SSRIs). The risk is assumed to be particularly high with short half-life drugs such as paroxetine and venlafaxine. Continuing to breast feed and then ‘weaning’ by switching to mixed (breast/bottle) feeding may help reduce the severity of reactions</td>
</tr>
<tr>
<td>When taken in late pregnancy, SSRIs may increase the risk of persistent pulmonary hypertension of the new-born</td>
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</table>

Bipolar illness during pregnancy and postpartum
- The risk of relapse during pregnancy if mood stabilising medication is discontinued is high; one study found that bipolar women who were euthymic at conception and discontinued mood stabilisers were twice as likely to relapse and spent 5 times as long in relapse illness than women who continued mood stabilisers.
- The risk of relapse after delivery is hugely increased: up to eight-fold in the first month post-partum
- The mental health of the mother influences foetal well-being, obstetric outcome and child development

The risks of not stabilising mood include:
- harm to the mother through poor self-care, lack of obstetric care or self-harm
- harm to the foetus or neonate (ranging from neglect to infanticide)

Treatment with mood-stabilisers
- Lithium completely equilibrates across the placenta. Although the overall risk of major malformations in infants exposed in-utero has probably been overestimated, lithium should be avoided in pregnancy if possible. Slow discontinuation before conception is the preferred course of action because abrupt discontinuation is suspected of worsening the risk of relapse. The relapse rate post-partum may be as high as 70% in women who discontinued lithium before conception. If discontinuation is unsuccessful during pregnancy – restart and continue
- Lithium use during pregnancy has a well-known association with the cardiac malformation Ebstein’s anomaly (relative risk is 10–20 times more than control, but the absolute risk is low at 1:1000). The period of maximum risk to the foetus is 2–6 weeks after conception, before many women know that they are pregnant. The risk of atrial and ventricular septal defects may also be increased.
- If lithium is continued during pregnancy, high-resolution ultrasound and echocardiography should be performed at 6 and 18 weeks of gestation
- In the third trimester, the use of lithium may be problematic because of changing pharmacokinetics: an increasing dose of lithium is required to maintain the lithium level during pregnancy as total body water increases, but the requirements return abruptly to pre-pregnancy levels immediately after delivery. Lithium plasma levels should be monitored every month during pregnancy and immediately after birth. Women taking lithium should deliver in hospital where fluid balance can be monitored and maintained
- Neonatal goitre, hypotonia, lethargy and cardiac arrhythmia can occur

Most data relating to carbamazepine and valproate come from studies in epilepsy, a condition associated with increased neonatal malformation. These data may not be precisely relevant to use in mental illness.
- Both carbamazepine and valproate have a clear causal link with increased risk of a variety of foetal abnormalities, particularly spina bifida. Both drugs should be avoided, if possible, and an antipsychotic prescribed instead. Valproate confers a higher risk than carbamazepine. Although 1 in 20 women of child bearing age who are in long term contact with mental health services are prescribed mood stabilising drugs, awareness of the teratogenic potential of these drugs amongst psychiatrists is low.
- Valproate monotherapy has also been associated with an increased relative risk of atrial septal defects, cleft palate, hypospadias, polydactyly and craniosynostosis, although absolute risks are low (K).
- Where continued use of valproate or carbamazepine is deemed essential, low-dose monotherapy is strongly recommended, as the teratogenic effect is probably dose-related. NICE recommends that the dose of valproate should be limited to 1000mg/day.
- Vulnerability to valproate-induced neural tube defects may be genetically determined via genes that code for folate metabolism/handling.
- Ideally, all patients should take folic acid (5 mg daily) for at least a month before conception (this may reduce the risk of neonatal neural tube defects). Note, however, that some authorities recommend a lower dose, presumably because of a risk of twin births.
- Use of carbamazepine in the third trimester may necessitate maternal vitamin K supplementation.
- Data for lamotrigine suggest a low risk of foetal malformations when used as monotherapy, although a substantially increased risk of cleft palate has been reported. Clearance of lamotrigine seems to increase radically during pregnancy. NICE suggest that lamotrigine should not be routinely prescribed in pregnancy.

### Recommendations – bipolar disorder in pregnancy

| For women who have had a long period without relapse, the possibility of switching to a safer drug (antipsychotic) or withdrawing treatment completely before conception and for at least the first trimester should be considered |
| The risk of relapse both pre- and post-partum is very high if medication is discontinued abruptly. |
| Women with severe illness or who are known to relapse quickly after discontinuation of a mood-stabiliser should be advised to continue their medication following discussion of the risks |
| No mood-stabiliser is clearly safe. Women prescribed lithium should undergo level 2 ultrasound of the foetus at 6 and 18 weeks’ gestation to screen for Ebstein’s anomaly. Those prescribed valproate or carbamazepine (both teratogenic) should receive prophylactic folic acid to reduce the incidence of neural tube defects, and receive appropriate antenatal screening tests |
| If carbamazepine is used, prophylactic vitamin K should be administered to the mother and neonate after delivery |
| Valproate (the most teratogenic) and combinations of mood-stabilisers should be avoided |
| Lamotrigine may be associated with cleft palate |
| NICE recommends the use of mood-stabilising antipsychotics as a preferable alternative to continuation with a mood-stabiliser |
| In acute mania in pregnancy use an antipsychotic and if ineffective consider ECT |
| In bipolar depression during pregnancy use CBT for moderate depression and an SSRI for more severe depression |

### Epilepsy during pregnancy and post-partum

- In pregnant women with epilepsy, there is an increased risk of maternal complications such as severe morning sickness, eclampsia, vaginal bleeding and premature labour. Women should get as much sleep and rest as possible and comply with medication (if prescribed) in order to minimise the risk of seizures.
- The risk of having a child with minor malformations may be increased regardless of treatment with antiepileptic drugs (AEDs).

The risks of not treating epilepsy are as follows:

- If seizures are inadequately controlled, there is an increased risk of accidents resulting in foetal injury. Post-partum the mother may be less able to look after herself and her child.
- The risk of seizures during delivery is 1–2%, potentially worsening maternal and neonatal mortality.

### Treatment with anticonvulsant drugs

It is established that treatment with anticonvulsant drugs increases the risk of having a child with major congenital malformation to two- to three-fold that seen in the general population. Congenital heart defects (1.8%) and facial clefts (1.7%) are the most common congenital malformations. Both carbamazepine and valproate are associated with a hugely increased incidence of spina bifida at 0.5–1% and 1–2%, respectively. The risk of other neural tube defects is also increased. In women with epilepsy, the risk of foetal malformations with carbamazepine is 2.3%; with lamotrigine, 3%; and with valproate, 7.2%. Higher doses (particularly doses of valproate exceeding 1000 mg/day) and anticonvulsant polypharmacy are particularly problematic. Cognitive deficits have been reported in older children who have been exposed to valproate in utero (L). Those exposed to carbamazepine may not be similarly disadvantaged.

Early data with lamotrigine and oxcarbazepine suggest a relatively lower risk of malformation, but confirmation is required (and note risk of cleft palate with lamotrigine).

Pharmacokinetics change during pregnancy, and there is marked inter-individual variation. Dosage adjustment may be required to keep the patient seizure-free. Serum levels usually return to pre-pregnancy levels within a month of delivery often much more rapidly. Doses may need to be reduced at this point.

Best practice guidelines recommend that a woman should receive the lowest possible dose of a single anticonvulsant.

### Recommendations – epilepsy in pregnancy

| For women who have been seizure free for a long period, the possibility of withdrawing treatment before conception and for at least the first trimester should be considered |
| No anticonvulsant is clearly safer. Valproate should be avoided if possible. Women prescribed valproate or carbamazepine should receive prophylactic folic acid to reduce the risk of neural tube defects. Prophylactic vitamin K should be administered to the mother and neonate after delivery |
| Valproate and combinations of anticonvulsants should be avoided if possible |
| All women with epilepsy should have a full discussion with their neurologist to quantify the risks and benefits of continuing anticonvulsant drugs during pregnancy |
**Sedatives**

Anxiety disorders and insomnia are commonly seen in pregnancy\(^{103}\). Preferred treatments are CBT and sleep-hygiene measures respectively.

- First-trimester exposure to **benzodiazepines** has been associated with an increased risk of oral clefts in new-borns\(^ {104}\), although two recent studies have failed to confirm this association\(^ {105}\) (M ref to follow – hopefully in press).
- Benzodiazepines have been associated with pylorostenosis and alimentary tract atresia\(^ {105}\); replication of these findings is required.
- There is an association between benzodiazepine use in pregnancy, low birth weight and pre-term delivery\(^ {105}\) (G).
- Third-trimester use is commonly associated with neonatal difficulties (floppy baby syndrome)\(^ {106}\).
- **Promethazine** has been used in hyperemesis gravidarum and appears not to be teratogenic, although data are limited.
- NICE recommends the use of low dose chlorpromazine or amitriptyline.

**Rapid tranquillisation**

There is almost no published information on the use of rapid tranquillisation in pregnant women. The acute use of short-acting benzodiazepines such as lorazepam and of the sedative antihistamine promethazine is unlikely to be harmful. Presumably, the use of either drug will be problematic immediately before birth. NICE also recommends the use of an antipsychotic but do not specify a particular drug\(^ {10}\). Note that antipsychotics are not generally recommended as a first line treatment for managing acute behavioural disturbance (see section on acute behavioural disturbance).

<table>
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<th>Recommendations – psychotropics in pregnancy</th>
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<td><strong>Psychotropic group</strong></td>
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<td><strong>Antidepressants</strong></td>
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<td><strong>Antipsychotics</strong></td>
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<td><strong>Sedatives</strong></td>
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References

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Further reading
NICE guidance (reissued April 2007) http://guidance.nice.org.uk/

Other sources of information

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(K) Jentink J et al. Valproic acid monotherapy in pregnancy and major congenital malformations. NEJM 2010,362;2185-93