

# Graylands Hospital Drug Bulletin

## Psychotropics and Pregnancy

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Psychotropic medication can have effects on fertility and on the developing foetus. Exposure during pregnancy is associated with potential obstetric, teratogenic, neurobehavioural and neonatal risks of toxicity.<sup>1</sup> These risks must be weighed up against the risks associated with not treating the mother's mental illness and her ability to care for the infant after birth.<sup>1</sup>

The use of psychotropic medications during pregnancy is considered appropriate in clinical situations where the risk of prenatal drug exposure is outweighed by the risk of relapse resulting from drug discontinuation.<sup>1</sup>

Due to ethical concerns, there are no controlled clinical trials focussing on the use of medications in pregnancy. Data is usually retrospective and often relies on prescription databases, teratology services, birth registries or population records of congenital defects.<sup>2</sup> Research on psychotropic medications is also limited due to the difficulty controlling for confounding factors such as diagnosis, maternal age, use of alcohol and other substances, smoking, genetic history and timing of drug exposure.<sup>3</sup>

### Foetal effects of drugs

The developing foetus may be adversely affected by exposure to drugs and environmental chemicals.<sup>4</sup> The stage of development of the foetus and the nature and concentration of the drug or chemical agents are the major determinants for the resultant effect.<sup>4</sup>

The foetus is at greatest risk of drug and chemical induced anatomical malformations during the first three months of gestation. This risk is also dose related.<sup>4</sup>

Intellectual, social and functional development can also be adversely affected by drug administration during pregnancy. These manifestations may be subtle, unexpected and typically occur in the second and third trimesters.<sup>5</sup>

### Prolactin effects on fertility

Drugs affecting prolactin levels, including the first generation antipsychotics, risperidone, paliperidone and amisulpride,<sup>6</sup> can temporarily reduce fertility if the prolactin level is elevated. The prolactin elevating effect of these antipsychotics is transient

and usually dose related.<sup>6</sup> If the medication is ceased or if the dose is reduced, fertility can return.

Elevated prolactin can reduce fertility in both males and females, as well as also causing a loss of libido and an inability to reach orgasm or ejaculate.<sup>7</sup>

Table 1: Relative risk of prolactin elevation for antipsychotics<sup>5, 6</sup>

	Prolactin elevation
<b>First-Generation Antipsychotics</b>	
Chlorpromazine	+++
Flupenthixol	+++
Fluphenazine	+++
Haloperidol	+++
Pericyazine	+++
Trifluoperazine	+++
Zuclopenthixol	+++
<b>Second-Generation Antipsychotics</b>	
Amisulpride	+++
Aripiprazole	-
Asenapine	+/-
Clozapine	-
Olanzapine	+
Paliperidone	+++
Quetiapine	-
Risperidone	+++
Sertindole	+/-
Ziprasidone	+/-

### Antipsychotics

People with schizophrenia are more likely to have minor physical anomalies than the general population, and psychotic illness itself during pregnancy is an independent risk factor for congenital malformations and perinatal mortality.<sup>6</sup>

### First-Generation Antipsychotics

First generation antipsychotics are generally considered to have minimal risk of teratogenicity,<sup>6</sup> though data is limited and not consistent.

Reviews have concluded that **phenothiazines** (chlorpromazine, fluphenazine, trifluoperazine, pericyazine) are not teratogenic.

**Chlorpromazine** (Australian category C in pregnancy) has been used in psychosis and the prevention of nausea and vomiting during

pregnancy, with no apparent increase in malformations. However, use near term should be avoided due to risks of maternal hypotension and adverse effects in the newborn.

There is one case report describing multiple anomalies with fluphenazine, though the mother also took other medications.<sup>4</sup> Overall, most evidence suggests fluphenazine is not teratogenic, but extrapyramidal and withdrawal symptoms have been noted in the neonate.<sup>4</sup>

Case reports have described three incidences of limb defects in infants exposed to haloperidol (category C) during the first trimester, though potential association requires further study.<sup>4</sup> Use in late pregnancy may cause extrapyramidal effects in the neonate.<sup>8</sup>

There are only two reports describing the use of flupenthixol (category C) during pregnancy,<sup>4</sup> with no evidence of teratogenicity. Flupenthixol crosses the placenta with foetal serum levels about one quarter that of the mother's.<sup>9</sup> Due to the lack of data, the safety of flupenthixol during pregnancy has not been established.<sup>8</sup>

There are no reports in the literature regarding the use of zuclopenthixol (category C) in pregnancy.<sup>4, 8</sup>

## Second-Generation Antipsychotics

### Amisulpride (category C)

No published information on amisulpride administration during pregnancy is currently available.<sup>10</sup> Amisulpride can significantly increase prolactin serum levels therefore could affect fertility.<sup>6</sup>

### Aripiprazole (category C)

There are four case reports in the literature of aripiprazole use during pregnancy, with no major malformations reported.<sup>8, 11-14</sup> One neonate developed unexplained tachycardia necessitating caesarean section at full term.<sup>12</sup> One patient was taking aripiprazole at the time of conception,<sup>13</sup> and one other patient started aripiprazole treatment at 8 weeks gestation.<sup>11</sup>

### Asenapine (category C)

There are no reports describing the use of asenapine in human pregnancy.

### Clozapine (category C)

There have been a number of case reports outlining the safety, course and outcome of pregnancy in women treated with clozapine.<sup>1</sup> The use of clozapine during pregnancy appears to present no increased risk of malformation, however gestational diabetes and neonatal seizures may be more likely to occur.<sup>6</sup>

There have also been reports of spontaneous

abortion, foetal death following clozapine overdose in the mother, neonatal hypocalcaemia, congenital blindness and large for gestational age babies, but there was no consistent pattern of malformations.<sup>4, 8</sup> Because of the potential effect of Clozapine on stem cells, Clozapine is not recommended in pregnancy or breastfeeding.

### Olanzapine (category C)

Regarding the use of second-generation antipsychotics during pregnancy, there is most data for olanzapine.<sup>6</sup> Lower birth weight, gestational diabetes and macrosomia have been reported.<sup>5</sup> Olanzapine appears to be relatively safe in regards to congenital malformations.<sup>6</sup>

### Paliperidone (category C)

Paliperidone can increase prolactin levels and reduce fertility in women taking the medication. There are no cases of paliperidone therapy in human pregnancy reported, but no increase in malformations was reported in animal studies.<sup>8</sup> Paliperidone is the major active metabolite of risperidone, which has been used in human pregnancy.<sup>4, 8</sup>

### Quetiapine (category C)

There have been several case reports of quetiapine use throughout gestation with no major malformations reported, although on several occasions other psychotropic medications were also used.<sup>8, 10</sup> Data is still limited but currently available information indicates that quetiapine does not increase the risk of major malformations.

### Risperidone (category C)

Limited data regarding the use of risperidone in pregnancy indicates that it is not a major teratogen.<sup>6</sup> Reports describe rates of adverse events following risperidone use during pregnancy and foetal anomalies that were consistent with rates in the general population.<sup>1</sup>

Little information is available regarding the use of risperidone long-acting injection (LAI) during pregnancy. One case report describing the use of risperidone LAI 25mg every 2 weeks resulted in a normal pregnancy with no abnormalities or development problems.<sup>8</sup>

Drug-induced hyperprolactinaemia may reduce fertility in women taking risperidone.

### Ziprasidone (category C)

There are four case reports in the literature outlining the use of ziprasidone in pregnancy. Two of these cases (ziprasidone 40mg/day plus citalopram 60mg/day and ziprasidone 160mg/day plus fluphenazine 2.5mg/day) reported no neonatal complications.<sup>15, 16</sup>

The third case involved an infant born with a cleft palate whose mother took ziprasidone during the entire pregnancy (40-120mg/day), with diazepam taken occasionally.<sup>17</sup>

There is also a case of an infant born with mild midface hypoplasia, hypoplastic nails, hypoplastic fingertips, bilateral 5<sup>th</sup> fingers clinodactyly and symmetric growth deficiency. It was postulated that this was possibly due to ziprasidone-induced ventricular arrhythmia in the neonate and subsequent brain hypoxia.<sup>18</sup>

## Antidepressants

Untreated depression during pregnancy appears to carry substantial perinatal risks, which are either direct risks to the foetus or risks secondary to unhealthy maternal behaviours. These risks include suicidal ideation, increased risk of miscarriage, hypertension, preeclampsia, low birth weight and a sixfold increase in the risk for postpartum depression.<sup>19</sup>

### Selective Serotonin Reuptake Inhibitors (SSRIs)

SSRIs are the most frequently prescribed antidepressant class in pregnancy. They are associated with reduction in birth weight, though not all studies show this association.<sup>20</sup>

**Paroxetine** (category D) has been specifically associated with cardiac malformations, particularly after high dose treatment (>25mg/day) and during the first trimester.<sup>6</sup> Not all studies, however, have replicated this finding.<sup>6, 19</sup>

There may also be an association with **sertraline** (category C) and an increased risk of septal defects.<sup>21-23</sup>

Several studies<sup>24</sup> have looked at the association between SSRIs and persistent pulmonary hypertension of the newborn (PPHN). PPHN is a rare illness that affects approximately 1.9 per 1,000 live births.<sup>25</sup> The existing literature consists of six studies that identified 50 infants with PPHN among an estimated 25,000 who were exposed to SSRIs.<sup>25</sup> Three studies found no increased risk of PPHN associated with SSRI exposure. One study found an increased risk only if the SSRI was used in the second half of pregnancy, and the other two studies examined the same population (the latter of these with additional information) and reported overall relative risks of 3.44 and 3.57.<sup>25</sup>

PPHN is estimated to be fatal in approximately 9% of cases, but no deaths have been reported in infants exposed to SSRIs in utero.<sup>25</sup> Currently, the evidence supporting the link between SSRIs and PPHN is weak.<sup>25</sup>

### Serotonin and Noradrenaline Reuptake Inhibitors (SNRIs)

**Venlafaxine** (category B2) is not expected to increase the risk of congenital anomalies but

transient and mild neonatal complications have been reported.<sup>8</sup> Withdrawal symptoms have been noted in neonates exposed to venlafaxine late in pregnancy.<sup>8</sup> The major active metabolite of venlafaxine, **desvenlafaxine** (category B2), has no reports regarding use in pregnancy.

**Duloxetine** (category B3) has been used by a limited number of pregnant women without an increase in the risk of congenital anomalies.<sup>8</sup>

### Tricyclic Antidepressants (TCAs)

TCAs do not appear to be associated with an increased risk of major malformations.<sup>5, 6, 20</sup> The use of TCAs in the third trimester is well known to cause neonatal withdrawal effects such as agitation, irritability, seizures and respiratory distress.<sup>6</sup>

TCAs have not shown to affect postnatal development of the child.<sup>5, 6</sup>

### Monoamine oxidase inhibitors (MAOIs)

**Phenelzine** (Category B3) and **tranylcypromine** (category B2) have been suspected of decreasing uterine blood flow and increasing the risk of adverse pregnancy outcomes.<sup>8</sup> MAOIs are best avoided during pregnancy due to their potential vasoconstrictive effects and the availability of antidepressant treatments with more evidence for use in pregnancy.<sup>8</sup>

### Other antidepressants

**Mirtazapine** (category B3) has not been reported to increase the risk of congenital anomalies, though the literature only contains limited reports pertaining to its use in pregnancy.<sup>8</sup>

The use of **reboxetine** (category B1) in pregnancy has been scarce, however there are no reports of an increased risk of birth defects.<sup>26</sup>

There are only five case reports describing the use of **moclobemide** (category B3) in pregnancy in the literature, all of which reported normal outcomes.<sup>8</sup>

Electroconvulsive therapy (ECT) has long been regarded as a safe and effective treatment in severe depression in pregnancy.<sup>20</sup>

There are no reports in the literature regarding the use of **agomelatine** (category B1) during pregnancy.

### Mood stabilisers

The risk of relapse both pre- and post-partum is very high if mood stabilising medication is discontinued. No mood stabiliser is clearly safe, and antipsychotics indicated in bipolar disorder may be preferable alternatives in women who are pregnant or planning to become pregnant. Most data relating to the anticonvulsants are from studies in epilepsy,

a condition known to be associated with increased neonatal malformation.<sup>6</sup>

### Lithium (category D)

Lithium equilibrates across the placenta and has a well-established association with the cardiac malformation, Ebstein's anomaly. The relative risk is 10-20 times more than those not taking lithium, but the absolute risk is low at about 1:1000. The maximum risk to the foetus occurs 2-6 weeks after conception. If lithium is used during pregnancy, high-resolution ultrasound and foetal echocardiography should be performed at 6 and 18 weeks gestation.<sup>6</sup>

The pharmacokinetics of lithium can also change in the third trimester, with pregnant women often requiring a higher dose to maintain adequate lithium levels. This occurs because total body water increases during this period, but lithium requirements return to pre-pregnancy levels immediately after delivery.<sup>6</sup>

### Sodium valproate (category D)

Sodium valproate is considered a teratogen and is associated with an increased risk of neural tube defects, craniofacial anomalies, limb abnormalities and cardiovascular malformations.<sup>3, 27</sup> Large studies have reported incidences of congenital malformations ranging from 6% to nearly 18%.<sup>8</sup>

Most case reports and studies of valproate use in pregnancy have involved women with epilepsy, which is also known to increase the risk of anomalies in the newborn.<sup>27</sup> Developmental delay has also been reported in infants whose mothers used valproate during pregnancy.<sup>3, 27</sup>

For the treatment of mental illness, valproate should be avoided in pregnancy if possible.<sup>6</sup> If patients need to continue it during pregnancy, it is recommended they take folic acid 5mg daily four weeks prior to and 12 weeks after conception to reduce the risk of neural tube defects.<sup>27</sup>

### Carbamazepine (category D)

Carbamazepine is also linked to an increased risk of congenital malformations. The teratogenic risks are similar to valproate, but generally occur less frequently and are less severe.<sup>3</sup> Foetal carbamazepine syndrome includes symptoms such as a short nose, long philtrum, epicanthal folds and fingernail hypoplasia.<sup>3</sup>

Folate supplementation, 5mg/day, is recommended 4 weeks prior to and 12 weeks after conception. Foetal vitamin K deficiency can also occur, therefore oral vitamin K is recommended in the last month of pregnancy and the neonate should receive vitamin K following delivery.<sup>3, 27</sup>

### Lamotrigine (category D)

Data from pregnancy registers do not indicate a

substantial increase in the risk of major congenital malformations following first trimester use of lamotrigine, although a limited number of registries have reported an increase in the risk of isolated oral cleft malformations.<sup>27</sup>

Folic acid supplementation at 5mg/day is recommended for women taking lamotrigine who are pregnant or planning to become pregnant.<sup>8, 27</sup>

## Benzodiazepines

Anxiety disorders and insomnia are common in pregnancy, and the preferred treatment options are cognitive behavioural therapy and sleep hygiene.<sup>6</sup>

Early studies indicated first trimester exposure to benzodiazepines was associated with an increased risk of oral clefts in the newborn, though later studies have failed to confirm this.<sup>3, 6</sup> Third trimester use is associated with withdrawal symptoms and floppy baby syndrome, which includes respiratory depression, hypothermia and feeding problems.<sup>3, 6</sup>

It is recommended to avoid benzodiazepines during pregnancy. If treatment is required, shorter-acting benzodiazepines used on a when required basis may be acceptable later in pregnancy, but use in the first trimester should be avoided if possible.<sup>5</sup>

Zolpidem (category B3) and zopiclone (category C) have been used in limited numbers of pregnant women with no increased incidence of major malformations.<sup>8</sup>

## Conclusion

There are many complex issues surrounding the use of psychotropic medications during pregnancy.<sup>1</sup> As with other drugs, the decision of whether or not to start or continue a psychotropic medication must be based on the latest available information and an individual assessment of probable risks and benefits.<sup>6</sup>

The safety of psychotropics cannot be clearly established as they have not been robustly studied during pregnancy.<sup>6</sup> If medications are needed, ideally the patient will be treated with monotherapy, at the lowest effective dose and the agent used should be selected on the basis of existing safety data.<sup>3</sup>

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References available on request

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