

# 12 - Chapter 7

## Prescribing in pregnancy and breastfeeding

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# 01 - Drug choice in pregnancy

## Drug choice in pregnancy

The Maudsley® Prescribing Guidelines in Psychiatry, Fifteenth Edition. David M. Taylor, Thomas R. E. Barnes and Allan H. Young. © 2025 David M. Taylor. Published 2025 by John Wiley & Sons Ltd. Chapter 7 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 major malformation in the newborn is 2–3% (approximately 1 in 40 pregnancies).<sup>1</sup> Lifestyle factors, such as smoking cigarettes, poor diet and drinking alcohol during pregnancy, can have adverse consequences for the fetus. Pre-pregnancy obesity increases the risk of neural tube defects and is associated with risk factors for the mother. Psychiatric illness during pregnancy is an independent risk factor for congenital malformations, stillbirths and neonatal deaths<sup>2</sup> and perinatal mental disorders are associated with a broad range of negative child outcomes, many of which can persist into late adolescence.<sup>3</sup> Severe mental illness is also associated with increased risk of obstetric near misses (life-threatening obstetric complications).<sup>4</sup> The safety of psychotropics in pregnancy cannot be clearly established because robust, prospective trials are unethical and long-term observational studies are challenging to undertake. Data are derived from database studies (many of which fail to control for confounders such as the impact of maternal mental illness, use of illicit drugs and alcohol, smoking, obesity and other medications), limited prospective data from teratology information centres and published case reports. For many drugs, the perceived association or otherwise with adverse outcomes changes over time, as more information is gathered and analysed. The patient's view of risks and benefits has paramount importance and needs to be informed by up-to-date evidence. Clinicians should be aware of the importance of prescribing medication to women with a severe mental illness. Perinatal suicides are notable for being associated with lack of active treatment, specifically the lack of treatment with psychotropic medication.<sup>5</sup> The American College of Obstetricians and Gynecologists (ACOG) warns against withholding or discontinuing medications for mental health conditions because of pregnancy or lactation status alone.<sup>6</sup> Box 7.1 provides a brief summary of the relevant issues and evidence available in early 2024. Prescribing in pregnancy and breastfeeding

714 The Maudsley® Prescribing Guidelines in Psychiatry CHAPTER 7 Box 7.1 General principles of prescribing in pregnancy In all women of child-bearing potential ■ ■ Always discuss the possibility of pregnancy – half of all pregnancies are unplanned<sup>7</sup> ■ ■ Avoid using drugs that are contraindicated during pregnancy (notably valproate, topiramate and carbamazepine). If use of these drugs is unavoidable then women should be made fully aware of their teratogenic properties

even if not planning pregnancy. In addition, the prescriber should confirm the presence of an effective and stable long-term contraceptive plan If mental illness is newly diagnosed in a pregnant woman ■ ■Consider non-pharmacological interventions ■ ■Try to avoid all drugs in the first trimester (when major organs are being formed) unless benefits clearly outweigh risks (i.e. if non--drug treatments are not effective/appropriate) ■ ■Use an established drug and use the lowest effective dose ■ ■Review current medication regimen to ensure there is a clear indication for each drug and that ineffective drugs are stopped If a woman taking psychotropic drugs is planning a pregnancy ■ ■Consideration should be given to discontinuing treatment if the woman is well and at low risk of relapse, after a careful review of her history ■ ■Discontinuation of treatment for women with severe mental illness (SMI) and at a high risk of relapse is generally unwise but consideration should be given to switching to a low-risk drug. However, be aware that switching drugs may increase the risk of relapse. Any changes must be made with caution and considered in the context of the woman's illness history and previous response to treatment ■ ■Drug-induced hyperprolactinaemia may prevent pregnancy. Consider switching to an alternative drug if hyperprolactinaemia occurs and a pregnancy is planned ■ ■For women with SMI, pre-conception advice from a perinatal psychiatrist should be sought to ensure that women are aware of their risk of relapse in the perinatal period and are able to discuss a prospective perinatal care plan If a woman taking psychotropic medication discovers that she is pregnant ■ ■Abrupt discontinuation of treatment post-conception is unwise for women with SMI and at a high risk of relapse. Relapse may ultimately be more harmful to the mother and child than continued, effective drug therapy ■ ■Consider continuing with current (effective) medication rather than switching, to minimise the risk of relapse and the number of drugs to which the fetus is exposed ■ ■Valproate (if prescribed as a mood stabiliser) must be stopped immediately ■ ■Early pregnancy can be associated with noticeable changes in mood, therefore it may be necessary to review the medication plan at this stage to ensure symptoms are well controlled If the patient smokes (smoking is more common in pregnant women with psychiatric illness<sup>8</sup>) ■ ■Smoking has been associated with the greatest proportion of excess risk of poor pregnancy outcomes<sup>9</sup> ■ ■Always encourage switching to nicotine replacement therapy. Referral to smoking cessation services is mandated by NICE in the UK ■ ■Vaping is probably safer than tobacco smoking but is not without risk. Nicotine replacement is probably safer than vaping<sup>10</sup> ■ ■Stopping smoking can increase plasma levels of certain drugs (e.g. clozapine)

# 02 - Psychosis during pregnancy and postpartum

## Psychosis during pregnancy and postpartum

Prescribing in pregnancy and breastfeeding CHAPTER 7 Psychosis during pregnancy and postpartum Pregnancy does not protect against psychotic relapse and psychosis during pregnancy predicts postpartum psychosis.<sup>13</sup> The incidence of postpartum psychosis is 0.1–0.25% in the general population (around 1–2 psychiatric hospitalisations per 1000 births). Women with bipolar disorder have an increased risk of postpartum psychosis with around one in five experiencing a psychotic relapse postpartum.<sup>14</sup> There is a high risk of relapse in women with a family history of postpartum psychosis or a personal history of postpartum psychosis.<sup>15</sup> The risk of postpartum psychosis for women with a previous episode of illness, a diagnosis of bipolar disorder type 1 or schizoaffective disorder, and genetic loading for postpartum psychosis, bipolar 1 or schizoaffective disorder, can be as high as 50%. The mental health of the mother in the perinatal period influences fetal well-being, obstetric outcome and child development. The risks of not treating psychosis include harm to the mother and harm to the fetus or neonate (ranging from neglect to infanticide). First-generation antipsychotics ■ ■ Some specific malformations have been reported with individual agents. However, first-generation antipsychotics (FGAs) are unlikely to be major teratogens.<sup>16</sup> ■ ■ Most initial data originated 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 the absence of clear clustering of congenital abnormalities, suggested that the condition being treated may be responsible rather than drug treatment. ■ ■ In a large American study including over a million women, no meaningful increase in the risk of major malformations or cardiac malformations was seen in 733 women prescribed an FGA.<sup>17</sup> A 2023 study of nearly 6.5 million women (6371 prescribed an FGA) in the USA and Nordic countries found that antipsychotics were not major In all pregnant women ■ ■ Ensure that parents are as involved as possible in all decisions ■ ■ Prescribe as few drugs as possible (both simultaneously and in sequence) and use the lowest effective dose ■ ■ Be prepared to adjust doses as pregnancy progresses and drug handling is altered. Dose increases are frequently required in the third trimester<sup>11</sup> when blood volume expands by around 30%. Plasma level monitoring may be helpful, where available. Hepatic enzyme activity also 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%<sup>12</sup> ■ ■ For patients with SMI, discuss with the patient a referral to specialist perinatal services ■ ■ Ensure adequate fetal screening by liaison with obstetric services ■ ■ Be aware of potential problems with individual drugs around the time of delivery ■ ■ Inform the obstetric team of psychotropic use and possible complications and where appropriate liaise with the neonatology team ■ ■ Monitor the neonate for withdrawal effects after birth ■ ■ Document all decisions (including the plan for medication)

716 The Maudsley® Prescribing Guidelines in Psychiatry CHAPTER 7 teratogens. In the same study, the authors reported an observed increased risk of cardiac malformations with (the rarely used) chlorprothixene, which the authors suggest should be viewed as a safety signal for further study.<sup>18</sup> ■ ■ There may be an association between haloperidol and limb defects (based on a small number of cases) but, if real, the risk is likely to be extremely low and it has not been replicated in larger studies. ■ ■ An increased risk of gestational diabetes<sup>19</sup> and possibly preterm birth<sup>20</sup> has been reported. A prospective study that included 284 women who took an FGA during pregnancy concluded that preterm birth and low birth weight were more common with FGAs than second-generation antipsychotics (SGAs) (or no antipsychotic exposure).<sup>21</sup> In addition to this, 20% of neonates exposed to an FGA in the last week of gestation experienced early somnolence and jitteriness. ■ ■ A higher risk of postpartum bleeding in vaginal delivery and a higher placenta to birth weight ratio has been reported.<sup>22</sup> ■ ■ Neonatal dyskinesia has been reported with FGAs.<sup>23</sup> ■ ■ Neonatal jaundice has been reported with phenothiazines.<sup>24</sup> ■ ■ An increased risk (greater in late pregnancy exposure) of neonatal withdrawal symptoms, neurological disorders and persistent pulmonary hypertension has been reported. The absolute risk is low, and the effects appear to be predominantly mild and transient.<sup>25</sup> Prolonged neonatal hospital stay after birth has been reported.<sup>22</sup> Second-generation antipsychotics ■ ■ Some specific malformations have been reported with individual agents. However, SGAs are unlikely to be major teratogens.<sup>16</sup> ■ ■ In a large American study, no meaningful increase in the risk of major malformations or cardiac malformations was seen in 9258 women prescribed an SGA. In this same study a small increase in absolute risk of malformations was seen with risperidone. The authors suggested that this particular finding should be interpreted with caution and be seen as a possible safety signal that requires further investigation.<sup>17</sup> In a separate study of 214 women taking an SGA, the absolute risk of major malformation was estimated to be 1.4% (1.1% in the control group).<sup>17</sup> Another American study which analysed data from the National Birth Defects Prevention Study reported an association between SGA use in early pregnancy and conotruncal heart defects, tetralogy of Fallot, anorectal atresia/stenosis and gastroschisis. The study included over 22,000 cases and over 11,000 controls. Notably (and this may explain the findings in relation to SGAs), women exposed to SGAs were more likely to report pre-pregnancy obesity, illicit drug use, smoking and alcohol use and use of other psychiatric medications during pregnancy.<sup>26</sup> A 2023 study of nearly 6.5 million women (21,751 prescribed an SGA) in the USA and Nordic countries reported that antipsychotics were not major teratogens. In the same study there was an observed increased risk of oral clefts with olanzapine and gastroschisis and brain anomalies with all SGAs, which the authors suggested should be viewed only as safety signals for further study.<sup>18</sup> ■ ■ A prospective study of 561 women who took an SGA during pregnancy concluded that SGA exposure was associated with increased birth weight, a modestly increased risk of cardiac septal defects (possibly due to screening bias or co-exposure to selective

Prescribing in pregnancy and breastfeeding CHAPTER 7 serotonin reuptake inhibitors [SSRIs]) and, as with FGAs, withdrawal effects in 15% of neonates.<sup>20</sup> ■ ■ Available data do not suggest that lurasidone is a major teratogen.<sup>27</sup> ■ ■ Olanzapine has been associated with lower birth weight and increased risk of intensive care admission,<sup>28</sup> a large head circumference<sup>29</sup> and macrosomia<sup>30</sup> (the last of these is consistent with the reported increase in the risk of gestational diabetes<sup>24,29,31,32</sup>). ■ ■ Neonatal seizures may be more likely to occur with clozapine<sup>31</sup> than with other SGAs. There is a single case report of maternal overdose resulting in fetal death<sup>24</sup> and there are theoretical concerns about the risk of agranulocytosis in the fetus/ neonate.<sup>24</sup> Overall, pharmacovigilance data do not indicate that clozapine is less safe in pregnancy than other antipsychotics.<sup>33</sup> Clozapine is included by the UK National Institute for Health and Care Excellence (NICE) in medications that may be prescribed in pregnancy. Lower mean adaptive behaviour scores have been reported in infants exposed to clozapine in utero compared with risperidone, quetiapine or olanzapine. A higher rate of disturbed sleep and lability were reported in clozapine- exposed infants in the same study.<sup>34</sup> On the balance of evidence available, clozapine should usually be continued during pregnancy. Clozapine plasma level monitoring may be beneficial,<sup>35</sup> especially if there are changes in smoking habits. ■ ■ An increased risk of gestational diabetes has been reported for SGAs<sup>19</sup> and possibly preterm birth,<sup>20</sup> low birth weight<sup>36</sup> and postpartum bleeding in vaginal delivery. The risk of gestational diabetes may be greatest with clozapine, olanzapine and quetiapine,<sup>37</sup> and aripiprazole may not be associated with an increased risk.<sup>38</sup> In a population-based study of over a million women, an increased risk of caesarean section, large for gestational age and preterm birth were reported in women prescribed an SGA compared with no antipsychotic. The risk of caesarean section and large for gestational age was higher with SGAs than with FGAs.<sup>39</sup> Maternal mental illness and lifestyle may also be important factors in the risk for gestational diabetes.<sup>40,41</sup> A lower risk with SGAs compared with FGAs has also been reported<sup>19</sup> and other studies did not report increased risk of metabolic complications.<sup>36</sup> ■ ■ An increased risk (greater in late pregnancy exposure) of neonatal withdrawal symptoms, neurological disorders and persistent pulmonary hypertension has been reported. The absolute risk is low, and the effects appear to be predominantly mild and transient.<sup>37</sup> ■ ■ Quetiapine has a relative low rate of placental passage.<sup>42,43</sup> One study of antipsychotic use in Finland showed a higher risk of increased postpartum bleeding in vaginal delivery, prolonged neonatal hospitalisation stay and a higher placenta to birth weight ratio with antipsychotics use. Quetiapine was the most commonly used antipsychotic in this study.<sup>22</sup> ■ ■ The manufacturers of cariprazine have advised against its use in pregnancy because of an increased risk of malformations noted in animal studies. It should probably be avoided. Antipsychotic use and longer-term neurodevelopment The effect of antipsychotics on longer-term neurodevelopment is unclear.<sup>44</sup> A small prospective case-control study reported that babies who were exposed to SGAs in utero had delayed cognitive, motor and social-emotional development at 2 and 6 months old but

718 The Maudsley® Prescribing Guidelines in Psychiatry CHAPTER 7 not at 12 months.<sup>45</sup> The clinical significance of this finding is unclear. No significant adverse effect on IQ or neurodevelopmental functioning was shown in a small study of school-aged children following exposure to antipsychotics during pregnancy.<sup>46</sup> A cohort study of 667,517 children did not show an association between maternal antipsychotic prescription and poorer standardised test performance in language and mathematics in schoolchildren.<sup>47</sup> Two large cohort studies have reported increased risk of attention deficit hyperactivity disorder (ADHD) and autism spectrum disorder (ASD) associated with maternal mental illness but not with prenatal antipsychotic

exposure.<sup>20,48</sup> A smaller study reported no increased risk of psychiatric disorders in children born to women who continued antipsychotics in pregnancy.<sup>49</sup> A 2022 birth cohort study found antipsychotics to not be causally associated with neurodevelopmental disorders although there was a safety signal for aripiprazole, which requires further study.<sup>50</sup> Recommendations for psychosis in pregnancy are outlined in Box 7.2.

**Box 7.2 Recommendations – psychosis in pregnancy**

- Overall, the 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. However, the high risk of adverse outcomes for the mother and child associated with untreated maternal illness should be noted
- Patients with a history of psychosis who are maintained on antipsychotic medication should be advised to discuss a planned pregnancy as early as possible
- Women should be supported to minimise the risks in pregnancy from smoking and alcohol and drug misuse. Women should be referred to appropriate services such as smoking cessation clinics and addictions services
- Drug-induced hyperprolactinaemia may prevent pregnancy. Consider switching to an alternative drug if hyperprolactinaemia occurs and a pregnancy is planned
- If a pregnant woman is stable on an antipsychotic and likely to relapse without medication, advise her to continue the antipsychotic.<sup>51</sup> Switching medication is generally not advised owing to the risk of relapse
- When initiating an antipsychotic consider using the antipsychotic that has previously worked best for the woman, after discussion of benefits and risks.<sup>43</sup> This may minimise fetal exposure by avoiding the need for higher doses and/or multiple drugs should relapse occur
- Be clear of the indication for each drug, use the lowest effective dose and prescribe as few drugs as possible both simultaneously and in sequence. Do not continue medication that is not effective
- Advise pregnant women taking antipsychotic medication about diet and monitor for excessive weight gain
- Women taking an antipsychotic during pregnancy should be monitored for gestational diabetes. In the UK, NICE recommends women are offered an oral glucose tolerance test
- In the UK, NICE recommends avoiding depot preparations in 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<sup>51</sup>
- The Australian Centre of Perinatal Excellence (COPE) recommends a 13- or 18–20-week ultrasound for women taking antipsychotics in the first trimester<sup>52</sup>
- Antipsychotic discontinuation symptoms can occur in the neonate (e.g. crying, agitation, increased suckling). This is thought to be a class effect.<sup>53</sup> When antipsychotics are taken in pregnancy it is recommended that the woman gives birth in a unit that has access to paediatric intensive care facilities.<sup>21</sup> Some centres used mixed (breast/bottle) feeding to minimise withdrawal symptoms
- Document all decisions

# 03 - Depression during pregnancy and postpartum<sup>545</sup>

## Depression during pregnancy and postpartum<sup>54–56</sup>

Prescribing in pregnancy and breastfeeding CHAPTER 7 Depression during pregnancy and postpartum<sup>54–56</sup> Approximately 10% of pregnant women develop or have a pre-existing depressive illness. Around a third of cases of postpartum depression begin before birth and there is a significant increase in new psychiatric episodes in the first 3 months after delivery. At least 80% of these are mood disorders, particularly severe depression. Women who have had a previous episode of depressive illness (postpartum or not) are at higher risk of further episodes during pregnancy and postpartum. The risk is highest in women with bipolar illness who are also at risk of mania or mixed affective episodes. There is some evidence that depression increases the risk of spontaneous abortion (miscarriage),<sup>57</sup> having a low birth weight or small for gestational age baby, or of preterm delivery, although effects are small.<sup>3,58,59</sup> The mental health of the mother influences fetal well-being, obstetric outcome and child development. The risks of not treating depression include harm to the mother through poor self-care, lack of obstetric care or self-harm and harm to the fetus or neonate (ranging from neglect to infanticide). Antidepressants Relapse rates are higher in those with a history of depression who discontinue medication compared with those who continue. One study found that 68% of women who were well on antidepressant treatment and stopped during pregnancy relapsed, compared with 26% who continued antidepressants.<sup>54</sup> Risk is likely to be highest for women with a history of severe and/or recurrent depression.<sup>60</sup> The rate of antidepressant withdrawal will also influence the risk of depressive relapse. Available data do not suggest an association between prenatal antidepressant use and neurodevelopmental disorders (after controlling for maternal illness and other confounders).<sup>61</sup> There is also some evidence that successful antidepressant use can be beneficial for child behavioural outcomes. A Danish study found that adverse outcomes were relatively more likely in

depressed women not taking antidepressants.<sup>62</sup> However, antidepressant exposure in pregnancy may be an important marker of the need for early screening and intervention. Tricyclic antidepressants ■ ■ Fetal exposure to tricyclics (via the umbilicus and amniotic fluid) is high.<sup>63,64</sup> ■ ■ Tricyclic antidepressants (TCAs) have been widely used throughout pregnancy without apparent detriment to the fetus.<sup>65–67</sup> ■ ■ A weak association between clomipramine use and cardiovascular defects cannot be excluded<sup>68</sup> and the European summary of product characteristics (SPC) for Anafranil states: ‘Neonates whose mothers had taken tricyclic antidepressants until delivery have developed dyspnoea, lethargy, colic, irritability, hypotension or hypertension, tremor or spasms, during the first few hours or days. Studies in animals have shown reproductive toxicity. Anafranil (i.e. branded clomipramine) is not recommended during pregnancy and in women of child-bearing potential not using contraception.’ The labels for other TCAs also contain a caution about withdrawal effects in neonates. One case of neonatal QT prolongation and torsades de pointes has been reported following maternal clomipramine use<sup>69</sup> and one case of Timothy syndrome

720 The Maudsley® Prescribing Guidelines in Psychiatry CHAPTER 7 (a disorder characterised by severe QT prolongation) in a newborn whose mother took amitriptyline in early pregnancy.<sup>70</sup> ■ ■ TCA use during pregnancy is associated with an increased risk of preterm delivery.<sup>65,66,71</sup> ■ ■ Use of TCAs in the third trimester is well known to produce neonatal withdrawal effects, such as agitation, irritability, seizures, respiratory distress and endocrine and metabolic disturbances.<sup>65</sup> These are usually mild and self-limiting. ■ ■ Little is known of the early developmental effects of prenatal exposure to tricyclics, although one small study detected no adverse consequences.<sup>72</sup> Limited data suggest in utero exposure to tricyclics has no effects on later development.<sup>72,73</sup> The authors of a study that reported an association between maternal antidepressant use and an increased risk of affective disorders in offspring<sup>74</sup> suggested the observed associations may be attributable to underlying parental psychopathology. There are no convincing data suggesting an association between prenatal antidepressant use and neurodevelopmental disorders<sup>61</sup> or ASD diagnoses or traits.<sup>75</sup> Selective serotonin reuptake inhibitors (SSRIs) ■ ■ SSRIs appear not to be major teratogens.<sup>65,67,76–78</sup> An association between prenatal SSRI use and congenital heart defects has been reported, with some studies reporting a higher risk with fluoxetine and paroxetine.<sup>79</sup> However, other studies have found no association between any SSRI and an increased risk of cardiac septal defects<sup>80–82</sup> nor any other heart defects<sup>83–87</sup> and it is suggested that mood disorders alone may be the cause of any increased risk of congenital heart defects.<sup>78</sup> ■ ■ One database study reported that fetal alcohol disorders were 10 times more common in those exposed to SSRIs in utero than in controls,<sup>88</sup> and that alcohol use during pregnancy (which may be used as self-medication for depression) is associated with an increased risk of cardiac defects in the fetus.<sup>68</sup> ■ ■ Sertraline appears to result in the least placental exposure.<sup>89</sup> ■ ■ There may be a small increased risk of preterm birth and low birth weight and lower Apgar scores and admission to neonatal intensive care units with SSRIs.<sup>78</sup> Maternal depression itself increases these risks.<sup>90,91</sup> Poor neonatal adaptation (including withdrawal symptoms) has been reported and risk may be increased with prematurity<sup>92</sup> and increasing dose, and may be higher with other SSRIs than sertraline.<sup>93</sup> ■ ■ SSRIs may increase the risk for persistent pulmonary hypertension of the newborn. The absolute risk appears to be small and more modest than previously estimated.<sup>94</sup> The risk may exist only in late pregnancy exposure<sup>95</sup> and may be lower with sertraline.<sup>96</sup> ■ ■ Gestational hypertension, pre-eclampsia, placental abnormalities and postpartum haemorrhage have been reported with SSRI use. The risks appear to be small and it should be noted that

maternal depression itself increases the risk of these outcomes.<sup>78</sup> The UK Medicines and Healthcare products Regulatory Agency (MHRA) advises that healthcare professionals need to be aware of the small increased risk of postpartum haemorrhage with SSRI/serotonin-noradrenaline reuptake inhibitor (SNRI) antidepressant use during the month before delivery. ■ ■ Data relating to neurodevelopmental outcome of fetal exposure to SSRIs are less than conclusive.<sup>72,73,97–100</sup> Depression itself may have more obvious adverse effects on development.<sup>72,101</sup> Some studies have reported a small increased risk of ASD.<sup>102–104</sup>

Prescribing in pregnancy and breastfeeding CHAPTER 7 However, larger studies have either failed to show this association after accounting for maternal illness and other demographic confounders<sup>75,105–107</sup> or have found it to be no longer statistically significant.<sup>108,109</sup> A large cohort study in 2022 reported that antidepressant use in pregnancy itself does not appear to increase the risk of neurodevelopmental disorders in children.<sup>61</sup> There is no reliable evidence indicating an increased risk of ADHD.<sup>91</sup> Poorer cognitive and gross motor development<sup>110</sup> and problems with speech and language,<sup>111–113</sup> behaviour<sup>114,115</sup> and fine motor control have been reported<sup>116</sup> but it is not clear whether or not this is a result of confounding. Authors of two separate studies, one reporting an association between antidepressant exposure in pregnancy and increased risk in the offspring of affective disorders<sup>74</sup> and the other describing higher rates of emotional disorders and antidepressant medication prescriptions,<sup>117</sup> have suggested the observed associations may be attributable to underlying parental psychopathology rather than direct exposure in utero. A 2023 study reported changes in brain morphology associated with SSRI exposure during pregnancy, some of which persisted into adolescence. The study did not assess clinical outcomes in the children and as such the significance of these findings is unclear.<sup>118</sup> Other antidepressants ■ ■ Despite a previously reported association between venlafaxine and increased risk of specific birth defects<sup>111</sup> including cardiac defects, anencephaly and cleft palate,<sup>119</sup> a 2022 meta-analysis concluded that available data do not indicate any SNRIs to be major teratogens.<sup>120</sup> An earlier observational study of 281 venlafaxine-exposed pregnancies did not find conclusive evidence that venlafaxine increased the risk of adverse pregnancy or fetal outcomes.<sup>121</sup> However, venlafaxine has been associated with neonatal withdrawal and poor neonatal adaptation syndrome,<sup>122</sup> babies being born small for gestational age<sup>123</sup> and postpartum haemorrhage.<sup>124</sup> The UK MHRA advises that healthcare professionals need to be aware of the small increased risk of postpartum haemorrhage with SSRI/SNRI antidepressant use during the month before delivery. SNRIs may be associated with an increased risk for persistent pulmonary hypertension of the newborn. The absolute risk appears to be low.<sup>96</sup> ■ ■ A large cohort study using propensity scores and several sensitivity analyses found duloxetine use in pregnancy may be associated with a small increase in the risk of postpartum hemorrhage,<sup>124</sup> and a case of suspected withdrawal syndrome in the newborn requiring hospitalisation has been reported.<sup>125</sup> However, no specific risks were identified with duloxetine in a study that prospectively followed 233 women through pregnancy and delivery.<sup>126</sup> A population-based observational study from Sweden and Denmark did not show an increased risk of major or minor congenital malformations or stillbirth with duloxetine.<sup>127</sup> ■ ■ Trazodone, bupropion (amfebutamone) and mirtazapine have few data supporting their safety.<sup>122,128,129</sup> A 2023 observational study did not find a significant difference in the risk of major congenital anomalies after first-trimester exposure to trazodone compared with SSRI exposure.<sup>130</sup> Available 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;<sup>131–133</sup> however this might be attributable to underlying psychiatric disease. A

2022 Danish study did not observe an

# 04 - Bipolar illness during pregnancy and postpart

## Bipolar illness during pregnancy and postpartum

722 The Maudsley® Prescribing Guidelines in Psychiatry CHAPTER 7 association between mirtazapine use and major congenital malformations, spontaneous abortion, stillbirth or neonatal death.<sup>134</sup> ■ ■ First-trimester exposure to bupropion may be associated with a slightly elevated risk of ventricular septal defects.<sup>135</sup> Bupropion exposure in utero has been associated with an increased risk of ADHD in young children.<sup>136,137</sup> Rather limited data suggest the absence of teratogenic potential with moclobemide<sup>138</sup> and reboxetine.<sup>139</sup> ■ ■ Monamine oxidase inhibitors should be avoided in pregnancy because of a suspected increased risk of congenital malformations and because of the risk of hypertensive crisis.<sup>140</sup> ■ ■ There is no evidence to suggest that electroconvulsive therapy (ECT) causes harm to either the mother or fetus during pregnancy<sup>141</sup> although general anaesthesia is of course not without risks. NICE recommends ECT for pregnant women with severe depression, severe mixed affective states or mania, or catatonia, whose physical health or that of the fetus is at serious risk. Box 7.3 summarises recommendations for treating depression in pregnancy. Bipolar illness during pregnancy and postpartum The risk of relapse during pregnancy if mood-stabilising medication is discontinued is high<sup>143</sup> and the risk of relapse after delivery is hugely increased. The mental health of the mother influences fetal 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, the need for hospital admission and harm to the fetus or neonate (ranging from neglect to infanticide). Box 7.3 Recommendations – depression in pregnancy ■ ■ Patients who are already receiving antidepressants and are at high risk of relapse are best maintained on the same antidepressant (assuming it is effective and well tolerated) during and after pregnancy ■ ■ Those who develop a moderate to severe or severe depressive illness during pregnancy should be treated with antidepressant drugs. If initiating an antidepressant during pregnancy or for a woman considering pregnancy, previous response to treatment must be taken into account. The antidepressant which has previously proved to be effective should be considered. For previously untreated patients, sertraline may be considered. ACOG recommends selective serotonin reuptake inhibitors (SSRIs) first line (with serotonin–noradrenaline reuptake inhibitors [SNRIs] a reasonable alternative) and if there is no pharmacotherapy history, sertraline or escitalopram is a reasonable first-line medication. COPE recommends SSRIs first line ■ ■ For moderate to severe perinatal depression with onset in the

third trimester, ACOG recommends consideration of brexanolone ■ ■Screen for alcohol use and be vigilant for the development of hypertension and pre-eclampsia ■ ■Women who take SSRIs or SNRIs late in pregnancy may be at increased risk of postpartum haemorrhage ■ ■When taken in late pregnancy, SSRIs may increase the risk of persistent pulmonary hypertension of the newborn. The absolute risk is very low ■ ■The neonate may experience poor neonatal adaptation syndrome or discontinuation symptoms ■ ■NICE in the UK<sup>142</sup> advises additional monitoring of the newborn of women who have taken an SSRI or SNRI antidepressant during pregnancy

Prescribing in pregnancy and breastfeeding CHAPTER 7 Mood stabilisers (non-antipsychotics) ■ ■Lithium completely equilibrates across the placenta.<sup>144</sup> Lithium exposure during pregnancy has been associated with an increased risk of congenital anomalies.<sup>145</sup> The risk is higher in the first trimester<sup>146</sup> and may be greater at higher doses.<sup>145</sup> Although the overall risk of major malformations in infants exposed in utero has probably been overestimated in the past, lithium should be avoided in pregnancy if possible. However, if lithium is the best drug for the woman and the drug most likely to keep her well, she should be advised of the increased risk but supported to stay on lithium. If discontinuation is planned, slow discontinuation before conception is the preferred course of action<sup>31,147</sup> because abrupt discontinuation worsens the risk of relapse. The relapse rate postpartum may be as high as 70% in women who discontinued lithium before conception.<sup>148</sup> ■ ■Lithium use during pregnancy has a well-known association with the cardiac malformation Ebstein's anomaly. However, more recent data suggest that the magnitude of the effect is much smaller than previously estimated.<sup>149,150</sup> Furthermore, a large surveillance study of 5.6 million births found an association of Ebstein's anomaly with maternal mental health problems generally rather than specifically with lithium.<sup>151</sup> The period of maximum risk to the fetus is 2–6 weeks after conception,<sup>152</sup> before many women know that they are pregnant. The risk of atrial and ventricular septal defects may also be increased.<sup>28</sup> If lithium is continued during pregnancy, high-resolution ultrasound and echocardiography should be performed in liaison with fetal medicine obstetric services. ■ ■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.<sup>153</sup> Women taking lithium should deliver in hospital where fluid balance can be monitored and maintained. ■ ■Lithium use in pregnancy has been associated with an increased risk of spontaneous preterm birth and large for gestational age neonates.<sup>154</sup> However, a large cohort study reported that lithium was not associated with placenta-mediated complications or preterm birth.<sup>155</sup> Lithium use may increase the risk of neonatal readmission within 4 weeks postpartum,<sup>146</sup> although a later study failed to replicate this finding.<sup>156</sup> Neonatal goitre, hypotonia, lethargy, cardiac arrhythmia, respiratory symptoms<sup>157</sup> and low Apgar scores<sup>158</sup> have been reported. ■ ■Lithium probably does not affect neonatal brain development.<sup>159</sup> ■ ■Most data relating to carbamazepine, valproate and lamotrigine 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 fetal abnormalities, particularly neural tube defects including spina bifida.<sup>160</sup> Both drugs should be avoided, and an antipsychotic prescribed instead. Valproate confers a higher risk (around 10% for major malformations) than carbamazepine<sup>161–163</sup> and should not be used in women of child-bearing age except where all other treatment has failed and when there is a long-term effective contraception plan. There is no evidence that folate protects against anticonvulsant-induced neural tube defects if given during pregnancy,<sup>164</sup> but it

may do so if given prior to conception (the neural tube is essentially

724 The Maudsley® Prescribing Guidelines in Psychiatry CHAPTER 7 formed by 8 weeks of pregnancy<sup>165</sup> before many women realise they are pregnant). However, folate supplementation may be beneficial with regard to early neurodevelopment and so should always be offered.<sup>164</sup> 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.<sup>166</sup> Valproate is also associated with a reduced head circumference in the neonate.<sup>167</sup> ■ ■ There appears to be a clear causal association between valproate use in pregnancy and motor and neurodevelopmental problems in exposed children. A review of studies by the European Medicines Agency showed that up to 40% of pre-school children exposed to valproate in utero experienced some form of developmental delay, including delayed walking and talking, memory problems, difficulty with speech and language and a lower intellectual ability. Poorer outcomes have been shown in language functioning, attention, memory, executive functioning and adaptive behaviour compared with carbamazepine and lamotrigine exposure. Lower IQs and an increased diagnosis rate of ASD are also reported.<sup>168,169</sup> Processing, working memory and learning deficits appear to be dose-related.<sup>170</sup> Decreased school performance has been associated with valproate use compared with children unexposed to anticonvulsants and with children exposed to lamotrigine.<sup>171</sup> ■ ■ Valproate use may increase risk of pre-eclampsia.<sup>172</sup> ■ ■ Where continued use of carbamazepine is deemed essential, low-dose (but effective) monotherapy is strongly recommended as the teratogenic effect is probably dose related.<sup>173,174</sup> Use of carbamazepine in the third trimester may necessitate maternal vitamin K. ■ ■ There is growing evidence that lamotrigine is safer in pregnancy than carbamazepine or valproate across a range of outcomes.<sup>164,168,175–177</sup> The risk of major malformations appears to be in the range reported for children not exposed to anticonvulsants.<sup>178</sup> Clearance of lamotrigine seems to increase radically during pregnancy<sup>179,180</sup> and then reduces postpartum<sup>181</sup> so frequent lamotrigine levels are necessary. ■ ■ Behaviour problems have been reported by parents of children exposed to lamotrigine in pregnancy.<sup>182</sup> Lamotrigine may be associated with an increased risk of autism.<sup>183</sup> However, available data suggest the effect of lamotrigine on neurodevelopment appears to not be significant.<sup>184</sup> ■ ■ Lower Apgar scores at birth have been reported with carbamazepine, valproate and topiramate. If an association exists, the absolute risk is low.<sup>185</sup> ■ ■ Major malformations,<sup>186</sup> specifically orofacial clefts, have been reported with topiramate.<sup>187</sup> The risk of oral clefts may be higher in women with epilepsy who use higher doses of the drug.<sup>188</sup> A large population study reported an increased risk of neurodevelopmental disorders, small for gestational age and congenital malformations<sup>189</sup> with prenatal topiramate exposure. Topiramate should not be used in pregnant women, and women of child-bearing age should take precautions to avoid getting pregnant.<sup>190</sup> ■ ■ The data for oxcarbazepine are not clear. A 2022 meta-analysis reported a small but not statistically significant increased risk of malformations in children exposed to oxcarbazepine.<sup>191</sup> Three studies in the same analysis reported an association with fetal/perinatal deaths. Because of some notable limitations in the studies included in this analysis, it is difficult to draw firm conclusions. ■ ■ Similarly, data for pregabalin are not clear.<sup>192</sup> However, based on a Nordic study<sup>193</sup> that showed a small increased risk of major malformations (compared with

Prescribing in pregnancy and breastfeeding CHAPTER 7 lamotrigine and duloxetine) the UK MHRA<sup>194</sup> and the manufacturers of pregabalin advise that women taking pregabalin be made aware of this risk and advised to use effective contraception. ■ ■ A large cohort study reported

that anticonvulsant mood stabilisers were not associated with placenta-mediated complications or preterm birth.<sup>170</sup> Recommendations for the treatment of bipolar disorder in pregnancy are outlined in Box 7.4.

**Box 7.4 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
- For women with a severe mental illness, discuss referral to perinatal services for pre-conception advice
- The risk of relapse both pre- and postpartum is very high if medication is discontinued abruptly
- No mood stabiliser is clearly safe. In the UK, NICE recommends the use of mood-stabilising antipsychotics as a preferable alternative to continuation with a mood - stabiliser
- Women with severe illness or who are known to relapse quickly after discontinuation of a mood-stabilising agent should be advised to continue their medication, following discussion of the risks. (This advice does not apply to valproate.) NICE recommends that if a woman taking lithium becomes pregnant, consider stopping lithium gradually over 4 weeks if she is well. Explain to her that there is a risk of relapse, particularly in the postnatal period, if she has bipolar disorder. If a woman taking lithium becomes pregnant and is not well or is at high risk of relapse, consider switching gradually to an antipsychotic or stopping lithium and restarting it in the second trimester (if the woman is not planning to breastfeed and her symptoms have responded better to lithium than to other drugs in the past) or continuing with lithium if she is at high risk of relapse and an antipsychotic is unlikely to be effective. If lithium is considered essential in a woman planning pregnancy, the woman should be informed of the risk of fetal heart malformations when lithium is taken in the first trimester and the risk of toxicity in the baby if lithium is continued during breastfeeding. In the UK, NICE recommends checking the plasma lithium levels every 4 weeks, then weekly from the 36th week, and to adjust the dose to keep plasma lithium levels in the woman's therapeutic range, ensuring the woman maintains an adequate fluid balance. The woman should give birth in hospital and be monitored by the obstetric team when labour starts, including checking plasma lithium levels and fluid balance because of the risk of dehydration and lithium toxicity. Lithium should be stopped during labour and plasma lithium levels checked 12 hours after the mother's last dose. ACOG recommends that pregnant patients taking lithium in the first trimester receive a detailed ultrasound examination in the second trimester to evaluate the fetal anatomy with a particular focus on cardiac anatomy. COPE recommends a 13- or 18–20-week ultrasound for women taking lithium or anticonvulsants in the first trimester
- Women prescribed lithium should undergo appropriate monitoring of the fetus in liaison with fetal medicine obstetric services to screen for Ebstein's anomaly
- NICE, ACOG and COPE strongly advise against the use of valproate in pregnancy. Valproate should be discontinued before a woman becomes pregnant. Women taking valproate who are planning a pregnancy should be strongly advised to gradually stop the drug because of the high risk of fetal malformations and adverse neurodevelopmental outcomes after any exposure in pregnancy. COPE recommends once the decision to conceive is made to stop valproate over 2–4 weeks, while adding in high-dose folic acid (5mg/day), which should continue for the first trimester.<sup>52</sup> In the UK, valproate may not be initiated in patients under 55 or continued in women of child-bearing potential unless two specialists agree and document that there is no other effective or tolerated treatment<sup>195</sup>

# 05 - Anxiety and insomnia during pregnancy and pos

## Anxiety and insomnia during pregnancy and postpartum

726 The Maudsley® Prescribing Guidelines in Psychiatry CHAPTER 7 Anxiety and insomnia during pregnancy and postpartum Anxiety disorders and insomnia are commonly seen in pregnancy.<sup>196</sup> Preferred treatments are cognitive behavioural therapy (CBT) and sleep-hygiene measures, respectively. Sedatives ■ ■ First-trimester exposure to benzodiazepines has been associated with specific malformations<sup>197</sup> such as oral clefts in newborns,<sup>198</sup> although other studies<sup>198–202</sup> have failed to confirm this association. Benzodiazepine use in pregnancy may be a marker for cardiac and total malformation risk.<sup>203</sup> ■ ■ Benzodiazepine use in pregnancy has been associated with caesarean delivery, spontaneous abortion, neonatal intensive care admission, neonatal ventilatory support, low birth weight, preterm delivery, small head circumference and small for gestational age babies.<sup>199,204–208</sup> Third-trimester use is commonly associated with neonatal difficulties (floppy baby syndrome).<sup>209</sup> A Taiwanese population-based study which accounted for confounding factors such as indication reported that benzodiazepine or Z drug use in early pregnancy was not associated with a substantial increase in the risk of stillbirth and preterm birth but there was an increased risk of small for gestational age. Exposure during late pregnancy was found to be associated with a substantially elevated risk of stillbirth and preterm birth.<sup>210</sup> ■ ■ Note that, in the UK, NICE advises that benzodiazepines are not offered to women in pregnancy and the postnatal period except for the short-term treatment of severe anxiety and agitation. It also suggests gradually stopping benzodiazepines in women who are planning a pregnancy, pregnant or considering breastfeeding.<sup>51</sup> ACOG recommends that benzodiazepines be avoided or prescribed sparingly as a treatment for perinatal anxiety. ■ ■ Promethazine has been used in hyperemesis gravidarum and appears not to be teratogenic, although data are limited. ■ ■ If valproate is the only drug that works for a particular woman, and this is seen as the only option for her during pregnancy, then the patient should be given a clear briefing of the risks and give written consent confirming that she understands the risk of malformations and developmental delays. Having said this, it is difficult to imagine any situation where the benefits of valproate outweigh the huge risks presented by using valproate in pregnancy ■ ■ NICE advises that carbamazepine not be offered to treat a mental health problem in women who are planning a pregnancy, pregnant or considering breastfeeding. NICE advises discussing the possibility of stopping carbamazepine if a woman is planning a pregnancy or becomes pregnant. If carbamazepine is used, prophylactic vitamin K

should be administered to the mother and neonate after delivery. ACOG recommends against discontinuing mood stabilisers (except for valproate) during pregnancy due to the risk of recurrence or exacerbation of mood symptoms ■ ■NICE advises if a woman is taking lamotrigine to check lamotrigine levels frequently during pregnancy and into the postnatal period because they vary substantially at these times ■ ■In acute mania in pregnancy use an antipsychotic and, if ineffective, consider electroconvulsive therapy ■ ■In bipolar depression during pregnancy use cognitive behavioural therapy for moderate depression and a selective serotonin reuptake inhibitor for more severe depression. Lamotrigine is also an option

06 - Attention deficit  
hyperactivity disorder (ADH

Attention deficit  
hyperactivity disorder  
(ADHD) in pregnancy

# 07 - References

## References

Prescribing in pregnancy and breastfeeding CHAPTER 7 ■ ■ Hypnotic benzodiazepine receptor agonists (Z drugs) are probably not associated with an increased risk of congenital malformations,<sup>211,212</sup> but an increased risk of premature birth, low birth weight and small for gestational age has been reported.<sup>211</sup> ■ ■ Zolpidem may be associated with an increased likelihood of caesarean section.<sup>213</sup> ■ ■ Available data do not appear to show an association between in utero benzodiazepine and/or Z drug exposure and neurodevelopmental disorders.<sup>214–216</sup> Attention deficit hyperactivity disorder (ADHD) in pregnancy Methylphenidate and amfetamines are probably not major teratogens.<sup>217,218</sup> A small increased risk of cardiac malformations has been reported with methylphenidate but is not seen with amfetamines.<sup>219</sup> There may be a small increased risk of spontaneous abortion with methylphenidate and a small increased risk of premature birth and low birth weight with amfetamines.<sup>218</sup> Modafinil may be associated with an increased risk of congenital malformations (including congenital heart defects, hypospadias and orofacial clefts).<sup>220,221</sup> In the UK, the MHRA advises that modafinil should not be used during pregnancy.<sup>220</sup> Women of child-bearing age must understand the risk of taking modafinil in pregnancy and should be advised to use effective contraception during treatment with modafinil and for 2 months after discontinuing treatment.<sup>220</sup> Available data do not show an increased risk of neurodevelopmental disorders in children exposed to ADHD medications in utero.<sup>222,223</sup> References

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# 08 - Drug choice in breastfeeding

## Drug choice in breastfeeding

# 09 - Infant exposure

## Infant exposure

# 10 - General principles of prescribing psychotropi

## General principles of prescribing psychotropics in breastfeeding

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The long-term benefits of breastfeeding on a child's physical health and cognitive development are well known. Women are generally encouraged to breastfeed for at least 6 months. One factor that may influence a mother's decision to breastfeed is the safety of a drug taken while breastfeeding. With some notable exceptions, most psychotropic drugs should be continued in breastfeeding women because of the benefits of breastfeeding and the lack of evidence of harm for most drugs. However, current evidence suggests that for a few drugs the woman should be advised not to breastfeed if such medications are the best and only option for her care. Data on the safety of psychotropic medication in breastfeeding are largely derived from small studies or case reports and case series. Reported infant and neonatal outcomes in most cases are limited to short-term acute adverse effects. Long-term safety cannot therefore be guaranteed for the psychotropics mentioned here. The information presented must be interpreted with caution with respect to the limits of the data from which it is derived and the need for such information to be regularly updated. There are two distinct clinical scenarios. In the first, the mother will have been taking the psychotropic drug(s) during pregnancy and often up until birth. In these people, the same psychotropic(s) should be continued during breastfeeding to mitigate withdrawal symptoms in the neonate (but see exceptions later). In the second, the mother is newly prescribed a psychotropic after the child has been born but wishes to breastfeed. Decisions in this scenario are rather more complex and the reader is referred to the tables in this section.

**Infant exposure** All psychotropics are excreted in breast milk to varying degrees. The most direct measure of infant exposure is, of course, infant plasma levels but these data are rarely available. Instead, many publications report only drug concentrations in breast milk and in maternal plasma. Maternal plasma levels of antipsychotics may be a useful estimate of infant exposure.<sup>1</sup> Breast milk drug concentrations can be used to estimate the daily infant dose (by assuming a milk intake of 150mL/kg/day). The infant weight-adjusted dose when expressed as a proportion of the maternal weight-adjusted dose is

known as the relative infant dose (RID). The RID should be used as a guide only, as values are estimates and these estimates vary widely in the literature for individual drugs. Drugs with an RID below 10% are usually regarded as safe in breastfeeding. Where measured, infant plasma levels below 10% of average maternal plasma levels have also been proposed as being safe in breastfeeding.<sup>2</sup>

**General principles of prescribing psychotropics in breastfeeding**

- The safety of individual drugs in breastfeeding should be taken into account when prescribing psychotropic medication for women considering pregnancy.
- Discussions about the safety of drugs in breastfeeding should be held as early as possible – ideally before conception or early in pregnancy. Decisions about the use of drugs in pregnancy should include the discussion about breastfeeding. Switching drugs at the end of pregnancy or in the days after birth is not advisable because of the high risk of relapse.

# 11 - Antidepressants in breastfeeding

## Antidepressants in breastfeeding

Prescribing in pregnancy and breastfeeding CHAPTER 7 ■ ■ Where a mother has taken a particular psychotropic during pregnancy and until delivery, continuation with the drug while breastfeeding will usually be appropriate (but see notable exceptions later), as this may minimise withdrawal symptoms in the infant. ■ ■ In each case the benefits of breastfeeding to the mother and infant must be weighed against the risk of drug exposure in the infant. Consider the infant's general health and gestational age at birth.<sup>3</sup> ■ ■ It is usually inappropriate to stop breastfeeding unless the currently prescribed drug is absolutely contraindicated in breastfeeding. As treatment of maternal mental illness is the priority, in such cases treatment should not be withheld but the mother should be advised to bottle feed with formula milk. ■ ■ When initiating a drug postpartum it is: ■ ■ important to consider the mother's previous response to treatment ■ ■ best to avoid a psychotropic with high reported infant plasma levels or a high RID ■ ■ important to consider the half-lives of the drugs: drugs with a long half-life can accumulate in breast milk and the infant. ■ ■ Neonates and infants do not have the same capacity for drug clearance as adults. Premature infants and infants with renal, hepatic, cardiac or neurological impairment are at a greater risk from exposure to drugs. ■ ■ Infants should be monitored for any specific adverse effects of the drugs as well as for abnormalities in feeding patterns and growth and development. ■ ■ Infant plasma levels should be monitored if adverse effects are noted or toxicity is suspected. ■ ■ Women receiving sedating medication should be strongly advised to not breastfeed in bed as they may fall asleep and roll onto the baby, with a potential risk of hypoxia to the baby. ■ ■ Sedation may affect women's ability to interact with their children. Women receiving sedating drugs should be monitored for this effect. ■ ■ Wherever possible: ■ ■ use the lowest effective dose ■ ■ avoid polypharmacy ■ ■ continue the regimen prescribed during pregnancy. Table 7.1 outlines recommendations for treatment with psychotropics in breastfeeding. Antidepressants in breastfeeding Table 7.2 provides information on individual drugs in breastfeeding based on available published data in late 2023. Manufacturers' formal advice on drugs in breastfeeding is available in the formal product literature or European Public Assessment Report for individual drugs. Table 7.2 does not include this advice (which is often uninformative), but instead uses primary reference sources. It is worth repeating that it is usually advisable to continue the antidepressant prescribed during pregnancy. Switching drugs postpartum for the purpose of

breastfeeding is usually not sensible. Table 7.2 should be used as a guide when initiating treatment postpartum. In each case previous response (and lack of response) to treatment must be considered.

# 12 - Antipsychotics in breastfeeding

## Antipsychotics in breastfeeding

# 13 - Mood stabilisers in breastfeeding

Mood stabilisers  
in breastfeeding

# 14 - Hypnotics in breastfeeding

## Hypnotics in breastfeeding

736 The Maudsley® Prescribing Guidelines in Psychiatry CHAPTER 7 Antipsychotics in breastfeeding Table 7.3 provides information on individual drugs in breastfeeding based on available published data in mid-2024. Manufacturers' formal advice on drugs in breastfeeding is available in the SPC or European Public Assessment Report for individual drugs. Table 7.3 does not include this advice (which is often uninformative), but instead uses primary reference sources. It is usually advisable to continue the antipsychotic prescribed during pregnancy. Switching drugs postpartum for the purpose of breastfeeding is usually not sensible. The exception to this is clozapine; clozapine should continue but breastfeeding should be avoided. Table 7.3 should be used as a guide when initiating treatment postpartum. In each case the previous response (and lack of response) to treatment must be considered. Mood stabilisers in breastfeeding Table 7.4 provides information on individual drugs in breastfeeding based on available published data in mid-2024. Manufacturers' formal advice on drugs in breastfeeding is available in the SPC or European Public Assessment Report for individual drugs. Table 7.4 does not include this advice (which is often uninformative), but instead uses primary reference sources. It is usually advisable to continue the mood stabiliser prescribed during pregnancy. Switching drugs postpartum for the purpose of breastfeeding is usually not sensible. The exception to this is lithium. Lithium should be continued but breastfeeding should not be permitted. Table 7.4 should be used as a guide when initiating treatment postpartum. In each case the previous response (and lack of response) to treatment must be considered. Hypnotics in breastfeeding Table 7.5 provides information on individual drugs in breastfeeding based on available published data in mid-2024. Manufacturers' formal advice on drugs in breastfeeding is available in the SPC or European Public Assessment Report for individual drugs. Table 7.5 does not include this advice (which is often uninformative), but instead uses primary reference sources. Table 7.1 Summary of recommendations. It is usually advisable to continue whichever drug has been used during pregnancy. When initiating a drug postpartum, previous response and tolerability should be considered Drug group Recommended drugs Antidepressants When initiating an antidepressant postpartum, sertraline may be considered. Other drugs may be used. See Table 7.2. Antipsychotics Women taking clozapine should be advised against breastfeeding and clozapine should be continued When initiating an antipsychotic postpartum, olanzapine or quetiapine may be considered. Other drugs may be used. See Table 7.3. Mood stabilisers Women taking lithium should be advised against breastfeeding and lithium should be continued When initiating a mood stabiliser postpartum, a mood-stabilising antipsychotic such as olanzapine or quetiapine may be considered. Other drugs may be used. See Table 7.4. Sedatives

Best avoided. Use a drug with a short half-life. See Table 7.5.

Table 7.2 Antidepressants in breastfeeding. Drug Infant plasma concentrations Relative infant dose (RID) Reported acute adverse effects in infant Reported developmental effects in infant

Agomelatine<sup>4,5</sup> Not assessed Not available None reported but not studied None reported but not studied

Brexanolone<sup>6</sup> Not assessed 1–2% None reported but not studied None reported but not studied

Bupropion<sup>5,7–14</sup> Undetectable or low 0.2–2% Two reports of seizure-like activity in 6-month-olds. In one of the cases the infant experienced sleep disturbance, severe emesis and somnolence. The infant plasma levels were below the level required for quantification. The mother was also taking escitalopram. None reported but not studied

Citalopram<sup>2,5,12,15–24</sup> Undetectable to up to 10% of maternal plasma levels Higher than for fluvoxamine, sertraline, paroxetine and escitalopram, but lower than for fluoxetine 3.56–5.37%<sup>5</sup> Sleep disturbance (which resolved on halving maternal dose), colic, decreased feeding, irritability and restlessness One case of irregular breathing, sleep disorder and hypo- and hypertonia; the Infant was exposed to citalopram in utero. Symptoms were attributed to withdrawal syndrome despite the mother continuing citalopram postpartum. None reported

In a study of 78 infants of mothers taking an SSRI or venlafaxine, no difference in weight was noted at 6 months compared with the ‘normative’ weight. In a study of 11 infants, normal neurodevelopment was observed up to 1 year. One of the children was unable to walk at 1 year, However, neurological status of the child was deemed normal 6 months later.

Duloxetine<sup>5,12,25–28</sup> <1% of maternal plasma levels <1% Dizziness, nausea and fatigue None reported but not assessed (Continued)

Drug Infant plasma concentrations Relative infant dose (RID) Reported acute adverse effects in infant Reported developmental effects in infant

Escitalopram<sup>5,12,14,29–34</sup> Undetectable or low 3–8.3% Necrotising enterocolitis in 5-day-old infant (necessitating intensive care admission and intravenous antibiotic treatment). Infant was exposed to escitalopram in utero. Symptoms were lethargy, decreased oral intake and blood in the stools. Seizure-like activity, sleep disturbance, severe emesis and somnolence in 6-month-old. Mother was also taking bupropion. None reported but not studied

Fluoxetine<sup>2,5,12,15,24,35–46</sup> Variable: can be >10% of maternal plasma levels. Highest reported levels of SSRIs 1.6–14.6% Colic, excessive crying, decreased sleep, diarrhoea, vomiting, somnolence, decreased feeding, hypotonia, moaning, grunting and hyperactivity One case of seizure activity at 3 weeks, 4 months and then 5 months. Mother was also taking carbamazepine. One case of tachypnoea, jitteriness, irritability, fever and compensated metabolic acidosis. Infant plasma levels were in the adult therapeutic range. The authors diagnosed serotonin syndrome. Mother was taking fluoxetine 60mg. Normal weight gain and neurological development have been reported for many infants. One retrospective study found lower growth curves compared with non-exposed infants. One case of a reduction in platelet serotonin

Fluvoxamine<sup>5,12,15,47–54</sup> Undetectable to up to half the maternal plasma level 1–2% Neonatal jaundice, severe diarrhoea, mild vomiting, decreased sleep and agitation None reported

In a study of 78 infants of mothers taking an SSRI or venlafaxine, no difference in weight was noted at 6 months compared with the ‘normative’ weight. MAOIs<sup>55,56</sup> No published data available at the time of writing

Isoniazid = 1.2–18% None reported None reported but not assessed Table 7.2 (Continued)

Drug Infant plasma concentrations Relative infant dose (RID) Reported acute adverse effects in infant Reported developmental effects in infant

Mianserin<sup>5,57</sup> Not assessed Not assessed None

reported None reported but not studied Mirtazapine<sup>5,12,58,59</sup> Undetectable or low. There was one case of higher mirtazapine plasma levels. Elimination rates may differ between individual infants 0.5–4.4% In a study of 54 infants exposed to mirtazapine in utero, the incidence of poor neonatal adaptation syndrome was significantly diminished in those who were breastfed. None reported In a study of eight infants, weights for three were observed to be between the 10th to 25th percentiles; all three were noted to also have a low birth weight. Moclobemide<sup>5,60,61</sup> Low 3.4% None reported None reported but not studied Paroxetine<sup>2,5,12,15,24,39,47,62–71</sup> Undetectable or low 0.5–2.8% Vomiting and irritability which were attributed to severe hyponatraemia In a study of 72 infants, adverse effects were noted in nine infants. Insomnia, restlessness and constant crying were most commonly reported. None reported In a study of 78 infants of mothers taking an SSRI or venlafaxine, no difference in weight was noted at 6 months compared with the ‘normative’ weight. Breastfed infants of 27 women taking paroxetine reached the usual developmental milestones at 3, 6 and 12 months, similar to a control group. Reboxetine<sup>5,12,72</sup> Undetectable or low 1–3% None reported In a study of four infants, three reached normal milestones. The fourth had developmental problems thought not to be related to reboxetine. Sertraline<sup>5,12,24,39,66,73–81</sup> Undetectable or low. There was one report of an unusually high infant serum level (half maternal serum level). The infant was reported to be ‘clinically thriving’ 0.5–3% Serotonergic overstimulation reported in preterm infant also exposed to sertraline in utero. Symptoms included hyperthermia, shivering, myoclonus, tremor, irritability, high-pitched crying, decreased suckling reflex and reactivity Withdrawal symptoms (agitation, restlessness, insomnia and an enhanced startle reaction) developed in a breastfed neonate, after abrupt withdrawal of maternal sertraline. The neonate was exposed to sertraline in utero. None reported In a study of 78 infants of mothers taking an SSRI or venlafaxine, no difference in weight was noted at 6 months compared with the ‘normative’ weight. (Continued)

Drug Infant plasma concentrations Relative infant dose (RID) Reported acute adverse effects in infant Reported developmental effects in infant Trazodone<sup>5,82,83</sup> Not assessed 2.8% None reported None reported Tricyclic antidepressants (TCAs)<sup>5,15,84–92</sup> Undetectable or low Nortriptyline Amitriptyline 1–3% Clomipramine Adverse effects have not been reported in infants exposed to nortriptyline, clomipramine, imipramine, dosulepin and desipramine through breast milk. Severe sedation and poor feeding reported with amitriptyline Poor suckling, muscle hypotonia, drowsiness and respiratory depression reported with doxepin None reported A study of 15 children did not show a negative outcome in regard to cognitive development in breastfed children 3–5 years postpartum. Venlafaxine<sup>5,12,24,39,66,93–100</sup> Undetectable to up to 37% of maternal plasma levels 6–9% (>10% reported in one case)<sup>101</sup> Lethargy, jitteriness, rapid breathing, poor suckling and dehydration in an infant also exposed in utero. Symptoms subsided over a week on breastfeeding. Authors suggested that breastfeeding may have helped manage infant withdrawal symptoms postpartum. None reported In a study of 78 infants of mothers taking an SSRI or venlafaxine, no difference in weight was noted at 6 months compared with the ‘normative’ weight. Vortioxetine 1.1–1.7%<sup>102</sup> 1.1–1.8% None reported None reported but not studied MAOI, monoamine oxidase inhibitor; SSRI, selective serotonin reuptake inhibitor. Table 7.2 (Continued)

Table 7.3 Antipsychotics in breastfeeding. Drug Infant plasma concentration Estimated daily infant dose as proportion of maternal dose (RID) Acute adverse effects in infant Developmental effects in infant Amisulpride<sup>5,96,103–105</sup> 10.5% of maternal plasma concentration\* 4.7–10.7% None

reported None reported Aripiprazole<sup>5,106–111</sup> (may lead to reduced milk supply)<sup>112,113</sup> 4% of maternal plasma concentration\* 0.9–8.3% None reported None reported Asenapine No published data available at the time of writing Brexpiprazole (may lead to reduced milk supply)<sup>112</sup> No published data available at the time of writing Butyrophenones<sup>5,15,39,84,104,114–117</sup> Not reported Haloperidol = 0.2–12% One case of hypersomnia, poor feeding and slowing in motor movements. Mother was also taking risperidone. The effects were noted when haloperidol dose was increased. Delayed development was noted in three infants exposed to a combination of haloperidol and chlorpromazine in breast milk. Normal development has also been reported. Cariprazine No published data available at the time of writing Clozapine<sup>5,15,39,84,115,118–121</sup> NB avoid 6.5% of maternal plasma concentration\* 1.4% Sedation, agranulocytosis, decreased sucking reflex, irritability, seizures and cardiovascular instability There is one report of delayed speech acquisition. The infant was also exposed to clozapine in utero. Iloperidone No published data available at the time of writing Lurasidone No published data available at the time of writing (Continued)

Drug Infant plasma concentration Estimated daily infant dose as proportion of maternal dose (RID) Acute adverse effects in infant Developmental effects in infant Lumateperone Published data not available Olanzapine<sup>5,15,39,104,122–134</sup> Undetectable or low One case of plasma levels decreasing over 5 months. The authors proposed that an infant's capacity to metabolise olanzapine 'developed rapidly' around the age of 4 months 1.0–1.6% Somnolence, drowsiness, irritability, tremor, insomnia, lethargy, poor suckling and shaking One case of jaundice and sedation. Infant was exposed in utero and had cardiomegaly. One case of lower developmental age than chronological age. Mother was taking additional psychotropic medication. One case of speech delay and one of motor developmental delay Two cases of failure to gain weight Normal development has also been reported. Paliperidone No specific data available (see risperidone) Phenothiazines<sup>5,15,84,114–116</sup> Variable Chlorpromazine = 0.3% Lethargy Delayed development in three infants exposed to a combination of chlorpromazine and haloperidol Pimavanserin No published data available at the time of writing Quetiapine<sup>5,97,131,135–144</sup> Undetectable 0.09–0.1% Excessive sleep. Mother was also taking mirtazapine and a benzodiazepine. In a small study of quetiapine augmentation of maternal antidepressant, there were two cases of mild developmental delays, thought not to be related to quetiapine. Table 7.3 (Continued)

Drug Infant plasma concentration Estimated daily infant dose as proportion of maternal dose (RID) Acute adverse effects in infant Developmental effects in infant Risperidone<sup>5,117,145–149</sup> Risperidone undetectable 9-hydroxyrisperidone low Risperidone = 2.8–9.1% 9-hydroxyrisperidone = 3.46–4.7% One case of hypersomnia, poor feeding and slowing in motor movements. Mother was also taking haloperidol. The effects were noted when haloperidol dose was increased. None reported Sertindole No published data available at the time of writing Sulpiride<sup>5,150–154</sup> Not reported 2.7–20.7% None reported None reported but not assessed Thioxanthenes<sup>5,15,116,155–157</sup> Not reported Zuclopenthixol = 0.4–0.9% Flupentixol = 0.7–1.75% None reported None reported for flupentixol Not assessed for zuclopenthixol Ziprasidone<sup>5,23,116,158</sup> Not reported 0.07–1.2% None reported None reported \*A proportion of the drug detected may have been due to placental transfer following in utero exposure. RID, relative infant dose.

Table 7.4 Mood stabilisers in breastfeeding. Drug Infant plasma concentration 1.1–7.3% Adverse effects have not been reported for a number of infants. One case of cholestatic hepatitis, one of transient hepatic dysfunction with hyperbilirubinaemia and elevated GGT. Adverse effects in the first case resolved after discontinuation of breastfeeding and the second resolved despite continued feeding. One case of seizure-like activity, drowsiness, irritability and high-pitched crying. Mother was taking multiple agents. Poor suckling, poor feeding and two cases of hyperexcitability Carbamazepine<sup>5,15,159–169</sup> Generally low although one report of an infant plasma level within adult therapeutic range Lamotrigine<sup>5,162,167,170–181</sup> Up to 48% of maternal plasma levels<sup>182</sup> 9.2–18.3% No adverse effects have been reported in a number of infants. Seven cases of thrombocytosis One case of a severe cyanotic episode (preceded by mild episodes of apnoea) requiring resuscitation. Neonatal serum concentration was in the upper therapeutic range. The infant was exposed in utero and the mother was taking a high dose (850mg/ day). One case of normocytic normochromic anaemia and asymptomatic neutropenia.<sup>183</sup> In Australia, the Centre for Perinatal Excellence (COPE) recommends close monitoring of the infant and a specialist neonatologist consultation where possible<sup>3</sup> Estimated daily infant dose as proportion of maternal dose (RID) Acute adverse effects in infant Developmental effects in infant None reported A prospective study of children of women with epilepsy found no adverse development at ages 6–36 months. The study assessed outcomes in children exposed to anticonvulsants in utero who were subsequently breastfed compared with those who were not. A study of 199 infants exposed to antiepileptic medications in utero and through breast milk failed to show a difference in IQ between breastfed and non-breastfed infants at the age of 3 years. A study of 181 children concluded that IQ was not adversely affected by anticonvulsant exposure through breast milk. No abnormalities reported A prospective study of children of women with epilepsy found that breastfeeding while taking an anticonvulsant was not associated with adverse development of infants at ages 6–36 months. The study assessed outcomes in children exposed to anticonvulsants in utero who were subsequently breastfed compared with those who were not. A study of 199 infants exposed to antiepileptic medications during breastfeeding failed to show a difference in IQ between breastfed and non-breastfed infants at the age of 3 years. The infants were exposed to antiepileptic medications in utero. A study of 181 children concluded that IQ was not adversely affected by anticonvulsant exposure in breast milk. Three cases of rash. In one case the rash was attributed to eczema, and to soy allergy in another. The third case resolved spontaneously.

Drug Infant plasma concentration Estimated daily infant dose as proportion of maternal dose (RID) Acute adverse effects in infant Developmental effects in infant Lithium<sup>184</sup> NB avoid Up to 57% of maternal plasma levels 12–30.1% Early feeding problems, increased urea, raised creatinine and non-specific signs of toxicity One case of elevated TSH. In utero exposure. One case of cyanosis, lethargy, hypothermia, hypotonia and a heart murmur. In utero exposure No adverse effects have been reported in others. None reported Topiramate<sup>185,186</sup> Undetectable to 20% of maternal plasma levels 3–35% Diarrhoea None reported but not assessed Valproate<sup>5,15,159–162,167,187,188</sup> <2% of maternal plasma levels 1.4–1.7% Thrombocytopenia and anaemia which reversed on stopping breastfeeding. In utero exposure A prospective study of children of women with epilepsy found that breastfeeding while taking an anticonvulsant was not associated with adverse development of infants at ages 6–36 months. The study assessed outcomes in children exposed to anticonvulsants in utero who were subsequently breastfed compared with those who were not. A study of 199 infants exposed to antiepileptic medications during breastfeeding failed to show a difference in IQ between breastfed and non-breastfed infants

at the age of 3 years. The infants were exposed to antiepileptic medications in utero. A study of 181 children concluded that IQ was not adversely affected by anticonvulsant exposure through breast milk. GGT, gamma-glutamyl transferase; RID, relative infant dose; TSH, thyroid-stimulating hormone.

Table 7.5 Hypnotics in breastfeeding. Drug Infant plasma concentration Estimated daily infant dose as proportion of maternal dose (RID) Acute adverse effects in infant Developmental effects in infant  
Benzodiazepines<sup>5,15,39,189-196</sup> Clonazepam: undetectable to 10% of maternal plasma levels<sup>197</sup>  
Clonazepam = 2.8% Diazepam = 0.88-7.1% Lorazepam = 2.6-2.9% Oxazepam = 0.28-1%  
Sedation, lethargy, weight loss and mild jaundice One case of persistent apnoea with clonazepam  
Restlessness and mild drowsiness with alprazolam In a telephone survey of 124 women two reported CNS depression in their breastfeeding neonates. One of the children was exposed to benzodiazepines in utero. No adverse effects have been reported in others. None reported but not studied Promethazine No published data available at the time of writing Zopiclone, zolpidem and zaleplon<sup>5,198-200</sup> Zolpidem: undetectable<sup>201</sup> Zopiclone and zaleplon: not reported Zaleplon = 1.5% Zopiclone = 1.5% Zolpidem = 0.02-0.18% None reported None reported but not studied RID, relative infant dose.

# 15 - Stimulants in breastfeeding

Stimulants in breastfeeding

# 16 - References

## References

Prescribing in pregnancy and breastfeeding CHAPTER 7 Stimulants in breastfeeding Table 7.6 provides information on individual drugs in breastfeeding based on available published data in mid-2024. Manufacturers' formal advice on drugs in breastfeeding is available in the SPC or European Public Assessment Report for individual drugs. Table 7.6 does not include this advice (which is often uninformative), but instead uses primary reference sources. It is usually advisable to continue the drug prescribed during pregnancy. Switching drugs postpartum for the purpose of breastfeeding is usually not sensible. Table 7.6 should be used as a guide when initiating treatment postpartum. In each case the previous response (and lack of response) to treatment must be considered. References

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11. Baab SW, et al. Serum bupropion levels in 2 breastfeeding mother-infant pairs. *J Clin Psychiatry* 2002; 63:910–911. Table 7.6 Stimulants in breastfeeding. Drug Infant plasma concentration Estimated daily infant dose as proportion of maternal dose (RID) Acute adverse effects in infant Developmental effects in infant Atomoxetine No published data

available at the time of writing Dexamfetamine 202 Undetectable to 14% of maternal plasma level 2.4 –10.6% None reported None reported but not assessed  
 Lisdexamfetamine No published data available at the time of writing  
 Methylphenidate 28,203–205 Undetectable 0.16–0.7% None reported None reported  
 Modafinil 206,207 Armodafanil = 1.5% 208 Modafanil not reported Armodafanil = 4.85% 208 Modafanil = 5.3% None reported None reported but not assessed RID, relative infant dose.

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