

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^{4,5} Not assessed Not available None reported but not studied None reported but not studied

Brexanolone⁶ Not assessed 1–2% None reported but not studied None reported but not studied

Bupropion^{5,7–14} 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^{2,5,12,15–24} 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%⁵ 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^{5,12,25–28} <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^{5,12,14,29–34} 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^{2,5,12,15,24,35–46} 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^{5,12,15,47–54} 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^{55,56} 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^{5,57} Not assessed Not assessed None reported

None reported but not studied

Mirtazapine^{5,12,58,59} 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^{5,60,61} Low 3.4% None reported

None reported but not studied

Paroxetine^{2,5,12,15,24,39,47,62–71} 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^{5,12,72} 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^{5,12,24,39,66,73–81} 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^{5,82,83} Not assessed 2.8% None reported

None reported

Tricyclic antidepressants (TCAs)^{5,15,84–92} 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^{5,12,24,39,66,93–100} Undetectable to up to 37% of maternal plasma levels 6–9% (>10% reported in one case)¹⁰¹ 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%¹⁰² 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^{5,96,103-105} 10.5% of maternal plasma concentration* 4.7-10.7% None reported None reported

Aripiprazole^{5,106-111} (may lead to reduced milk supply)^{112,113} 4% of maternal plasma concentration* 0.9-8.3% None reported None reported

Asenapine No published data available at the time of writing

Brexipiprazole (may lead to reduced milk supply)¹¹² No published data available at the time of writing

Butyrophenones^{5,15,39,84,104,114-117} 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^{5,15,39,84,115,118-121} 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^{5,15,39,104,122-134} 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^{5,15,84,114-116} 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^{5,97,131,135-144} 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^{5,117,145-149} 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^{5,150-154} Not reported 2.7-20.7% None reported None reported but not assessed

Thioxanthenes^{5,15,116,155-157} Not reported

Zuclopenthixol = 0.4-0.9% Flupentixol = 0.7-1.75% None reported None reported for flupentixol Not assessed for zuclopenthixol

Ziprasidone^{5,23,116,158} 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^{5,15,159–169} Generally low although one report of an infant plasma level within adult therapeutic range Lamotrigine^{5,162,167,170–181} Up to 48% of maternal plasma levels¹⁸² 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.¹⁸³ In Australia, the Centre for Perinatal Excellence (COPE) recommends close monitoring of the infant and a specialist neonatologist consultation where possible³ 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 Lithium¹⁸⁴ 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^{185,186} Undetectable to 20% of maternal plasma levels 3– 35% Diarrhoea None reported but not assessed Valproate^{5,15,159–162,167,187,188} <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 Benzodiazepines5,15,39,189–196 Clonazepam: undetectable to 10% of maternal plasma levels197 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 zaleplon5,198–200 Zolpidem: undetectable201 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.