

# Drugs in breastfeeding

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Handbook

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## SUMMARY

Most commonly used drugs are relatively safe for breastfed babies. The dose received via milk is generally small and much less than the known safe doses of the same drug given directly to neonates and infants.

Drugs contraindicated during breastfeeding include anticancer drugs, lithium, oral retinoids, iodine, amiodarone and gold salts.

An understanding of the principles underlying the transfer into breast milk is important, as is an awareness of the potential adverse effects on the infant.

Discussion with the mother about the possibility of either negative product information or ill-informed advice from others will reduce the confusion and anxiety that may be generated.

Good resources about medicines and breastfeeding are available and include state-based medicines information services.

## Introduction

Although the National Health and Medical Research Council recommends exclusive breastfeeding for around six months, continued alongside complementary food until a minimum of 12 months, current breastfeeding statistics show Australia falling well below these recommendations. While 96% of women start breastfeeding, exclusive breastfeeding rates drop off to 39% of babies at three months and 15% at five months.<sup>1</sup> Faced with these statistics, it is important to be able to give accurate advice on the safety of drugs so that breastfeeding is promoted whenever possible.

Most drugs are not of concern in breastfeeding.<sup>2-4</sup> In addition, most lactating women take few medicines, and then only occasionally. Further, even though virtually all drugs are transferred into breast milk to some extent, the amount of drug is usually small

and unlikely to cause an adverse effect on the baby. Considering the number of drugs available, relatively few known adverse effects occur in babies and it is generally not necessary to suspend breastfeeding because of the mother's medication. This concept is not new. It was suggested over 100 years ago that '... it is possible to show that drugs ... when given to a mother, rarely affect the milk injuriously, and almost never the babe to a marked degree'.<sup>5</sup>

Although the number of drugs available now is much greater, the same approach can apply. If ongoing medication use is necessary, only a few drugs warrant the cessation of breastfeeding (see Table). However, given the vulnerability of infants, vigilance is required.

## What affects the concentration of a drug in milk?

It is important to be aware of how drugs transfer into breast milk and what factors can influence this.

**Table** Examples of drugs contraindicated in breastfeeding

Drug	Comment
Amiodarone	Long half-life, iodine-containing molecule, and may affect thyroid function in infant
Antineoplastics	Leukopenia, bone marrow suppression
Gold salts	Rash, nephritis, haematological abnormalities
Iodine	High doses (>150 micrograms daily) lead to risk of infant hypothyroidism
Lithium	Breastfeeding only feasible with rigorous monitoring
Radiopharmaceuticals	Contact obstetric information service
Retinoids (oral)	Potential for serious adverse effects

### **Maternal plasma concentration**

Passive diffusion is the primary pathway by which drugs enter milk. There is a good concordance between the time-course of maternal plasma-drug concentration and milk-drug concentration. Maternal plasma concentration is also affected by the drug's distribution into different tissues. A high volume of distribution (as for sertraline) will contribute to a lower maternal plasma concentration and a subsequent lower concentration in milk.

### **Maternal plasma protein binding**

Transfer into breast milk is also influenced by the extent to which the drug is bound by maternal plasma proteins. Free unbound drug diffuses readily while highly protein-bound drugs like ibuprofen or warfarin (both 99% protein bound) are unable to diffuse in significant amounts.<sup>6</sup> Sertraline is highly protein bound (98%) so overall it will be minimally transferred to the breastfed baby.<sup>6</sup> By comparison, venlafaxine has much lower protein binding and so more of the drug will be present in milk.<sup>6</sup>

### **Size of the drug molecule**

Most drug molecules, including alcohol, nicotine and caffeine, are small enough to enter milk. Exceptions are drugs with high molecular weights such as heparins and insulin.

### **Degree of ionisation**

Drugs cross membranes in an un-ionised form. Milk is generally slightly more acidic (pH 7.2) than the mother's plasma (pH 7.4) so it attracts weak organic bases such as oxycodone and codeine.<sup>7</sup> Such drugs become ionised and 'trapped' in the milk. Conversely, weak organic acids such as penicillin tend to be ionised and held in maternal plasma.

### **Lipid solubility**

In addition to the passive diffusion into the aqueous phase, lipid-soluble drugs such as citalopram<sup>8</sup> may have co-secretion by dissolution in the fat droplets of milk.<sup>2</sup> In practical terms, this may not be of concern. It would not be an indication to change therapy if citalopram has been effective, but infant drowsiness should be monitored. Although the fat content of the milk varies according to infant age and phase of the feed, this is unlikely to impact on the choice of drug therapy.

### **Maternal pharmacogenomics**

A growing understanding of the influence of pharmacogenomics is well exemplified with codeine which is variably metabolised to morphine by the cytochrome P450 (CYP) 2D6 enzyme. The ultra-rapid metaboliser phenotype occurs in up to 10%

of Western Europeans and up to 30% of North Africans. Repeated codeine doses in these women produce significant amounts of morphine. Rapid transfer from maternal plasma to the milk may result in central nervous system depression and potentially infant death.<sup>9</sup> Codeine should be avoided during breastfeeding<sup>10</sup> and alternative analgesia is recommended, such as paracetamol or ibuprofen.

### **What influences the risk of adverse effects on the baby?**

If the baby is exposed to a drug in milk, several factors determine if there is an effect.

#### **Timing of the dose**

Feeding the baby just before the mother takes a drug results in the baby receiving the lowest possible drug concentration. However, this principle clearly does not apply for drugs with a long half-life, such as diazepam. For these drugs, there should be an even more rigorous assessment of whether they are needed.

#### **Toxicity**

Premature babies and neonates have a lower capacity to metabolise and excrete drugs.<sup>2</sup> In addition, for babies who may already have been exposed to a drug in utero just before delivery, further exposure via breast milk will augment the existing drug concentration.

The Table lists drugs that are contraindicated in breastfeeding. Some drugs are inappropriately regarded as unsafe. Metronidazole, despite unfounded fears of carcinogenicity and mutagenicity, is safe in breastfeeding for short-term use.<sup>11</sup> However, anecdotally, its bitter taste in milk may lead to fussiness in the feeding infant. Valproate is regarded as safe, especially in monotherapy when the risk of infant sedation is low.<sup>11</sup> Monitoring the infant for liver and platelet changes may be advisable.<sup>12</sup>

The immunosuppressant azathioprine is excreted into breast milk as an active metabolite 6-mercaptopurine. Cautious use is advised in lactating women, and monitoring of the infant for signs of immunosuppression and other toxicity is recommended.<sup>6,11,12</sup>

#### **Oral bioavailability**

The drug's presence in breast milk does not necessarily lead to significant exposure for the baby. The infant gut may degrade or destroy a drug, for example omeprazole (for which the standard formulation is enteric-coated). Gentamicin is given intravenously to the mother. As it is poorly absorbed orally by the baby, drug concentrations will not be reflected in infant plasma.

### Volume of breast milk

The amount of milk a baby receives varies. The estimated intake by an exclusively breastfed baby is 150 mL/kg/day. However, if the breast is being offered only as a comfort to an older baby, for example at night, the volume ingested is likely to be small.

### Relative infant dose

The relative infant dose is the dose received via breast milk (mg/kg/day) relative to the mother's dose (mg/kg/day). It is expressed as a percentage. A relative dose of 10% or above is the notional level of concern,<sup>6</sup> but this is rare. An example is lithium,<sup>6,12</sup> which is generally contraindicated in breastfeeding.<sup>13</sup>

### Age of infant

A review found that most adverse effects of drugs in breast milk occurred in newborns under two months and rarely in those older than six months.<sup>14</sup> An infant's metabolism and excretion capacity at birth is only a third of what it is at 7–8 months.<sup>15</sup>

### Drugs used to stimulate milk production

Domperidone and metoclopramide are galactagogues and have both been used off-label to stimulate prolactin and enhance milk supply. However, these drugs do not have high evidence of efficacy for this indication.<sup>11,16</sup> Also, there are concerns about the overuse of domperidone given that it may be prescribed on discharge from obstetric hospitals and used long term, sometimes at high doses. Non-pharmacological approaches to boost milk supply, such as correct advice, support and more frequent breastfeeding, are preferable.

### Practice points for prescribing in breastfeeding

- If a drug is needed, prescribe it at the lowest effective dose. Temporarily suspend breastfeeding (and express milk) for potentially toxic drugs, such as cytotoxics and radiopharmaceuticals (see Table). Reinstatement of a drug will be determined by its half-life. It may not be possible to continue breastfeeding if lengthy treatment with a toxic drug is needed.
- Select alternative routes or products to minimise systemic exposure in the mother. For example, choose a poorly absorbed fibre laxative over a stimulant laxative.
- Choose drugs with a relatively short half-life, such as sertraline rather than fluoxetine, to minimise drug exposure in milk.

- Advise the mother to feed the infant before taking her medicine so that the drug concentration in milk will be at its lowest. Reassure her that the drug will return to her bloodstream from the milk as her blood concentration falls and will not 'store' in the milk until the next feed. This advice does not apply to drugs with a long half-life. The need for these drugs should be reassessed, especially in the neonatal period.

### Advice on social drugs

Advise mothers to delay a glass of alcohol until after a feed and wait for two hours before the next feed to minimise infant exposure. Nicotine replacement therapy is not an absolute contraindication to breastfeeding and is preferable to smoking, although short-acting forms should be selected. Smoking, including passive smoking, has been associated with sudden infant death syndrome. High maternal intake of caffeine is associated with irritability and poor sleep patterns in the infant.

Breastfeeding in the context of illicit drug use is likely to be problematic. A follow-up study of one-year-old breastfed infants of mothers who used cannabis found some impairment in motor development, although the researchers found it difficult to determine whether in utero exposure was a greater influence.<sup>17</sup> Women should be encouraged to stop using cannabis and avoid exposure of the baby to second-hand smoke.

### Finding information and advice

If unsure, seek advice on the use of a drug during breastfeeding. There are a number of different information sources available.

### Drug information services

State-based obstetric drug information services provide detailed advice on the use of drugs during lactation and should be able to advise about past clinical experience with the drug (see Box).

### LactMed

LactMed<sup>11</sup> is a freely accessible, well-resourced and peer-reviewed online database that can be downloaded as an app for mobile devices. It is updated to keep pace with new information, including published studies and drug approvals. It also incorporates information on complementary treatments.

### Australian Medicines Handbook

The Australian Medicines Handbook (AMH)<sup>16</sup> also provides information on prescribing during lactation. It includes advice about drugs that may suppress lactation and those that are contraindicated or should be used with caution. However, lack of evidence of harm does not mean that a drug is safe.

## The Women's Pregnancy and Breastfeeding Medicines Guide

The Women's Pregnancy and Breastfeeding Medicines Guide, originally published in book format, is now available as an online subscription.<sup>12</sup> The online version is constantly updated, providing evidence-based recommendations on the use of medicines during pregnancy and breastfeeding.

### Product information

Be aware that the drug's product information sometimes contains advice that is contrary to recommended treatment.<sup>18</sup> An example is the treatment of mastitis with cephalexin: 'Alternative feeding arrangements for the infant should be considered.' Explanation should be given to the mother (and, if appropriate, her partner) that, while taking any antibiotic for mastitis, it is recommended to breastfeed more frequently and perhaps also express milk, to prevent stasis in the milk ducts and to maintain supply.

### Conclusion

Most commonly used drugs are relatively safe for breastfed babies. The dose received via milk is generally small and much less than the known safe doses of the drugs used in neonates and infants. Further, most lactating women take few medications and often only occasionally. For women on chronic medications, most can be reassured, but some drugs will be contraindicated and others not yet adequately studied. Good resources are available, including state-based drugs and medicines information services. ◀

Neil Hotham is a specialist editor for the Australian Medicines Handbook.

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## Box Obstetric drug information services in Australia

<b>Australian Capital Territory</b>	Medicines Information Service Canberra Hospital and Health Service Phone: 02 6244 3333
<b>New South Wales</b>	MotherSafe Royal Hospital for Women Phone: 02 9382 6539 Toll free (NSW): 1800 647 848
<b>Northern Territory</b>	Northern Territory Drug Information Centre Royal Darwin Hospital Phone: 08 8922 8424
<b>Queensland</b>	For health professionals: Queensland Medicines Advice and Information Service (QMAIS) Royal Brisbane and Women's Hospital Phone: 07 3646 7599 or 07 3646 7098
<b>South Australia</b>	SA Pharmacy Obstetric and Paediatric Medicines Information Service Women's and Children's Hospital Phone: 08 8161 7222
<b>Tasmania</b>	No drug information centre currently available
<b>Victoria</b>	Medicines Information Services Pharmacy Department, Royal Women's Hospital Phone: 03 8345 3190  Medicines Information Centre Monash Health Phone: 03 9594 2361
<b>Western Australia</b>	Drugs in Pregnancy and Breastfeeding Information Service King Edward Memorial Hospital Phone: 08 9340 2723

## FURTHER READING

**Alcohol**

Haastруп MB, Pottегård A, Damkier P. Alcohol and breastfeeding. *Basic Clin Pharmacol Toxicol* 2014;114:168-73.

**Antiepileptics**

Veiby G, Engelsen BA, Gilhus NE. Early child development and exposure to antiepileptic drugs prenatally and through breastfeeding: a prospective cohort study on children of women with epilepsy. *JAMA Neurol* 2013;70:1367-74.

**Benzodiazepines**

Kelly LE, Poon S, Madadi P, Koren G. Neonatal benzodiazepines exposure during breastfeeding. *J Pediatr* 2012;161:448-51.

**Codeine**

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**Galactogogues**

Forinash AB, Yancey AM, Barnes KN, Myles TD. The use of galactogogues in the breastfeeding mother. *Ann Pharmacother* 2012;46:1392-404.

**Ibuprofen**

Rigourd V, de Villepin B, Amirouche A, Bruneau A, Seraissol P, Florent A, et al. Ibuprofen concentrations in human mature milk--first data about pharmacokinetics study in breast milk with AOR-10127 "Antalait" study. *Ther Drug Monit* 2014;36:590-6.

**Olanzapine**

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**Oxycodone**

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**Skin preparations**

Butler DC, Heller MM, Murase JE. Safety of dermatologic medications in pregnancy and lactation: Part II Lactation. *J Am Acad Dermatol* 2014;70:417.e1-10.

**Tacrolimus**

Zheng S, Easterling TR, Hays K, Umans JG, Miodovnik M, Clark S, et al. Tacrolimus placental transfer at delivery and neonatal exposure through breast milk. *Br J Clin Pharmacol* 2013;76:988-96.