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USE OF MEDICINES IN BREASTFEEDING WOMEN

- **Most commonly used medicines can be used by breastfeeding women**
- **It is important to balance the benefits of medication for the mother and the benefits of continued breastfeeding for the mother and infant, against the limited or potential risk of medicine exposure to the infant**
- **Caution is advised when prescribing for mothers of premature or low birth weight infants, particularly when multiple medicines are required**
- **Useful medicines information resources are available for healthcare professionals (HCPs) on the use of medicines in breastfeeding women; where possible HCPs should provide practical recommendations about infant monitoring to breastfeeding women taking medicines**

INTRODUCTION

Breast milk contains bioactive components such as growth factors, immunoglobulins, cytokines and antimicrobial compounds.[1,2] **The benefits of breastfeeding for both infants (especially for premature infants) and mothers are well known.**[1-6] Breastfed babies have a lower risk of sudden infant death syndrome, allergy and acute infections, and in later life, improved cognitive development and a lower risk of obesity.[1,2,5,7] Mothers who have breastfed have a reduced risk of breast cancer, ovarian cancer, type 2 diabetes and hypertension.[1,2,5] The World Health Organisation recommends exclusive breastfeeding for the first 6 months of life, with the introduction of complementary foods at 6 months and continued breastfeeding until 2 years and beyond.[1] Ireland has the lowest rate of breastfeeding in Europe; at discharge from hospital only 48.6% of infants are exclusively breastfed, and only 6% of infants up to 6 months of age.[1]

Evidence suggests that up to 72% of breastfeeding women take some sort of medicine.[2,5] **Healthcare professionals (HCPs) play a major role in providing support and advice to breastfeeding women, including on the appropriate use of medicines.**[1-3,5,8]

This bulletin which updates a previous National Medicines Information Centre (NMIC) bulletin outlines the general principles to consider when prescribing for a lactating woman, reviews the use of some specific medicines in breastfeeding and identifies some useful medicines information resources.

GENERAL CONSIDERATIONS

Most commonly used medicines can be used by breastfeeding women, however it can be challenging for HCPs to identify which medicines are compatible and which pose potential risks.[1,3-5,9] As most medicines are not evaluated in breastfeeding women, the standard medicines information sources (e.g. Summary of Product Characteristics [SmPC]) may have limited information and therefore may not recommend use of a medicine in breastfeeding. Specialist lactation resources, however, are available with up to date information for most medicines (see useful resources section).[10-12] Currently there is more safety information available for the use of pharmacological medicines in breastfeeding compared to complementary medicines (e.g. herbal medicines).[5,13] Older medicines which have more safety information or experience of use are usually preferable.[3]

It is important to balance the benefits of medication for the mother and the benefits of continued breastfeeding for the mother and infant, against the limited or potential risk of medicine exposure to the infant.[3,5,14] Most medicines ingested by breastfeeding mothers pass into breast milk, however the amount of medicine is usually small and unlikely to cause an adverse effect on the infant;[15,16] there are relatively few contraindications to medicine use while breastfeeding (e.g. radiopharmaceuticals and chemotherapy).[2,3,5,14,16,17] **Breastfeeding rarely needs to be discouraged or discontinued when a mother requires a medicine, however each case needs to be assessed individually for benefit/risk and the individual medicine, infant and mother considered in the evaluation.**[2,17] Some medicines may require special consideration with monitoring of the infant advised, especially if the infant is preterm or has other health complications.[2,17]

Medicine factors: The potential risk of a specific medicine when used in a breastfeeding mother depends on factors including the dose, toxicity, pharmacokinetics, route and duration of administration of the medicine.[18,19] The concentration of a medicine in breast milk is impacted by many factors, as shown in table 1.

Table 1: Factors determining how much medicine enters breastmilk[2,3,15]

Factors include:	Effect
Maternal plasma concentration	In general as the maternal plasma level of a medicine increases, the breast milk level of the medicine increases
Maternal plasma protein binding	Medicines that are highly protein bound (e.g. ibuprofen and warfarin) are less likely to pass into breast milk, while those that are less protein bound (e.g. venlafaxine and atenolol) are more likely
Size of the molecule	Medicines with high molecular weight (e.g. heparins and insulin) are less likely to pass into breast milk
Lipid solubility	Medicines that are highly lipid soluble (e.g. diazepam) are more likely to pass into breast milk
Degree of ionisation	Breast milk is more acidic than plasma, therefore medicines with a high pH (e.g. oxycodone) may concentrate more in breast milk
Half-life	Medicines with long half-lives (e.g. benzodiazepines and fluoxetine) are more likely to accumulate in breast milk (and can also increase the risk of accumulation in the infant)

Once medicines pass into breast milk, other factors are important such as the oral bioavailability of the medicine to the infant; medicines with a low bioavailability (e.g. monoclonal antibodies, omeprazole, aminoglycosides) do

not enter the infant's bloodstream to a significant extent and are unlikely to cause systemic adverse effects, however they may affect the infant's gastrointestinal tract causing diarrhoea, constipation and rarely pseudomembranous colitis.[3] There are some medicines that are associated with potential adverse events, however the risks can be minimised by careful monitoring of the infant.[5] Medications that are used therapeutically in infants (e.g. paracetamol, ibuprofen, amoxicillin), are generally considered to be low risk when given to the breastfeeding mother.[2,3] **In cases where polypharmacy is required for maternal reasons, the risk of adverse effects may be increased (especially with sedating and psychoactive medicines), and the infant should be monitored closely.**

Infant factors: The most important factors to consider are the age, weight, maturity and overall health of the infant.[2,3] Newborns and especially premature infants are more at risk of adverse effects from some medicines, due to immaturity of the liver and kidneys and an immature blood-brain barrier.[2,3,18] Adverse events associated with medicine exposure via breast milk occur most often in infants <2 months (especially <1 month) and rarely in infants >6 months.[16] Older infants are at lower risk of adverse effects due to maturity of the hepatic enzymes and a reduced milk intake.[2]

The volume of breast milk that the infant is exposed to is an important consideration in evaluating risk; the estimated intake by an exclusively breastfed infant is 150mL/kg/day, however in early postpartum the amount of milk produced (30 to 100mL/day) may be so low that the clinical dose of drug transferred is low.[3,15] Infants that are breastfed once or twice a day are at very low risk.[3] Some information sources suggest that it may be possible to reduce infant exposure by giving the maternal dose immediately after the infant has been fed with the aim of avoiding feeding at peak milk concentrations.[4,19] This may be suitable for the administration of an immediate-release preparation (in the evening), however it may not be feasible for long-acting formulations or for multiple daily dosing regimens and may not be practical for the mother, especially where young infants are feeding frequently up to 2 hourly.[19] The risk reduction of this method is also not quantified.

A useful method for estimating the risk to the infant is the Relative Infant Dose (RID), calculated by dividing the estimated infant's dose via milk (mg/kg/day) by the mother's dose (mg/kg/day).[3] In general a RID of <10% is usually considered safe,[20] however this depends on the individual drug; for toxic drugs such as anticancer drugs a much lower RID should be considered in the evaluation of risk to the infant.[3] In addition, RID values may vary widely in the literature,[2,3,20] therefore **the RID should be used as a guide only and should not be used alone to evaluate risk.[2]**

Maternal factors: Due to concerns about the risk of medicine exposure to the infant via breast milk, women who require medication for acute or chronic conditions may discontinue breastfeeding or be less likely to breastfeed; furthermore, women may not take required medication in order to continue breastfeeding.[1-3,5,10,16] HCPs should discuss the benefits and risks associated with the medication and encourage the mother to continue breastfeeding, if it is reasonable to do so.[11] Aspects to consider include: **the severity of the condition being treated, whether the medication is for short-term or long-term use and the risk to the mother of not receiving medication.[3]** It may be appropriate to offer an alternative medication that may be safer in some cases, however this may not always be appropriate (e.g. women who are successfully treated on a particular antidepressant).[19] Women receiving sedating medication should be strongly advised not to breastfeed in bed as they may fall asleep and roll onto the infant.[20] It is important for women with chronic conditions (e.g. depression, hypertension) that discussions about the safety of medicines in breastfeeding take place as early as possible, ideally before conception or early in pregnancy.[20] Evidence suggests that breastfeeding women have less concerns about the safety of over-the-counter (OTC) and complementary medicines, even though there is less safety information available for complementary medicines.[5] The use of unnecessary medicines should be avoided and the mother should be advised to limit the use of OTC medications, and to seek advice if using them.[4]

Table 2 highlights some questions to ask when giving advice on medicines and breastfeeding.

Table 2: Questions to ask when giving advice on medicines and breastfeeding[21]*

Question	Comment
What medicine(s) is the mother currently taking?	Enquire about prescription, OTC and herbal medicines, and duration of therapy
What medicine is being considered and for what indication?	Consider benefit/risk for mother; is there an alternative that may be more appropriate in breastfeeding women
Is the mother already taking the medicine?	Switching to an alternative may not be appropriate (e.g. antidepressant)
Has the mother taken this medicine during pregnancy?	A separate risk assessment is required as not all medicines that are suitable or not suitable in pregnancy will be necessarily so in breastfeeding
How old is the infant? Is he/she premature or full-term?	The metabolism of medicines varies with the infant's age and maturity
Is the infant healthy or does he/she have conditions (including renal or hepatic dysfunction)?	This may impact on the infant's metabolism of the medicine that he/she is being exposed to
Is the infant already being prescribed a medicine?	Is there a possibility of a drug-drug interaction with other medicines that the infant may be taking?
Is the infant exclusively on breast milk? How often is the mother breastfeeding?	The risk assessment will vary depending on whether the infant is exclusively breastfed or being fed episodically

*table reproduced with the permission of the UK Drugs in Lactation Advisory Service (UKDILAS)

FREQUENTLY ASKED QUESTIONS ON THE USE OF MEDICINES IN BREASTFEEDING

The NMIC frequently receives enquiries from prescribers on the use of medicines in breastfeeding women; resources used to answer the enquiry include standard medicines information sources including the SmPC, specialist lactation sources and the recent literature (see table 4). The following examples cover some of the most common enquiries from primary care to the NMIC.

Use of antidepressants in breastfeeding women

Postpartum depression, which affects up to 20% of women can have devastating consequences for the mother and infant.[2,22-25] Antidepressants may be required when psychological and cognitive behavioural therapy are ineffective and in women with moderate to severe depression.[23,24,26] A growing body of evidence demonstrates negligible risk in infants exposed to the majority of antidepressants, particularly selective serotonin reuptake inhibitors (SSRIs).[24,27] The choice of antidepressant depends on the individual mother and infant; it is largely dictated by the antidepressant used during pregnancy and / or prior successful treatment with a specific antidepressant.[10,20,24,26] Abrupt cessation or switching of antidepressants is not recommended in the postpartum period due to concerns about a risk of relapse;[10,20,24,26] in addition, continuation of an antidepressant while breastfeeding may minimise withdrawal symptoms in the infant.[20] Women with depression may require additional support to establish and maintain breastfeeding.[2,10,26] The risks of breastfeeding while on an antidepressant in mothers of premature or

medically ill infants should be individually determined in consultation with the paediatrician.[24]

Selective serotonin reuptake inhibitors are usually considered first-line antidepressants in breastfeeding women (who are antidepressant naïve).[3,25,26] Sertraline, which has a short half-life and low passage into breast milk, is generally considered the SSRI of choice.[3,10,23,26-30] Citalopram and escitalopram are other options.[26,29] Fluoxetine would be the least preferred due to its long half-life,[3,26,27,29,30] however if the mother was benefiting from taking fluoxetine during pregnancy, continuation of the medication with infant monitoring is recommended.[2,3,10,26] Adverse effects reported in infants exposed to SSRIs (mainly fluoxetine and citalopram) include a collection of neurobehavioural symptoms such as infant irritability, hypertonia, jitteriness and poor feeding.[10,16,25,26,29] **Infants of breastfeeding women on SSRIs should be monitored for adverse effects including irritability, drowsiness and poor feeding.[3,26,30]**

Serotonin noradrenaline reuptake inhibitors (SNRIs): Of the SNRIs, most breastfeeding information is available for venlafaxine.[3,26,29] Most infants exposed to venlafaxine in breast milk have no reported adverse reactions, however there have been some reports of drowsiness and agitation.[26,29] There is less experience with the use of duloxetine in breastfeeding women.[3,26] **Infants should be monitored for sedation, irritability, poor feeding and weight gain.[3]**

Other antidepressants: Mirtazapine has minimal passage into breast milk and no reported adverse effects in the infant.[24,28,29,31] Tricyclic antidepressants (TCAs) are now less frequently used to treat depression because of their side effect profile.[26,30]

Practice points: Most antidepressants can be used in breastfeeding women.[26,29] In general, **the mother should be treated with an antidepressant that she has responded to already.[26]** In women who have not previously been treated with an antidepressant, sertraline is a first-line option.[20,26,29] **Infants should be monitored for any specific adverse effects of the drugs in addition to abnormalities in feeding patterns, growth and development.[20]**

Use of antihypertensives in breastfeeding women

Breastfeeding women may require antihypertensive medication; the choice depends on the mother, infant, and local/national guidelines.[32] Once-daily regimens should be used where possible.[10,12]

Angiotensin converting enzyme inhibitors (ACEIs) are often used first-line in hypertension.[12,33,34] The ACEIs with most breastfeeding data available are enalapril and captopril;[3,35,36] they are poorly excreted in breast milk and adverse effects have not been observed in breastfed infants.[3,10,28,29,35,36] Enalapril (once-daily formulation) is recommended by UK NICE as the antihypertensive of choice in women with hypertension in the postnatal period.[10,12] **Infants (especially premature and newborn) should be monitored for hypotension;[32] caution is recommended in breastfed premature infants due to possible renal toxicity.[3]** The teratogenic risks associated with ACEIs should also be considered for women who are planning a future pregnancy.

Calcium channel blockers (CCBs) may be used first-line in breastfeeding women,[33] especially in women of black African or Caribbean origin.[3,10,12] CCBs such as nifedipine and amlodipine enter breast milk, without apparent adverse effects in the breastfed infant.[3,10,28,29,33,35,36]

Beta blockers vary widely in terms of their potential effects on breastfed infants; those that have lower levels in breast milk and relatively low renal excretion, are considered to have less risks for the breastfed infant.[32,33] While beta blockers may not be the drugs of choice for hypertension,[29] beta blockers including propranolol, labetalol and metoprolol are recommended by some sources as suitable for breastfeeding women if required.[3,28,29,32,37] Atenolol and bisoprolol have a relatively low percentage of protein binding and long half-lives, therefore other beta blockers may be preferred.[28,29,33,37,38] **Infants (especially premature and newborn) of breastfeeding mothers on beta blockers should be monitored for signs of beta blockade especially bradycardia and hypoglycaemia.[32,37]**

Methyldopa is poorly excreted into breast milk and considered compatible with breastfeeding.[3,28,29,32,35] However, some sources recommend that it should be avoided or stopped within 2 days of delivery due to an increased risk of depression associated with its use.[34,35,39]

Breastfeeding women should avoid diuretics (may reduce breast milk production) and angiotensin receptor blockers (due to a lack of data).[3,12,36]

Practice points: Women with hypertension should be informed that they can still breastfeed, as most antihypertensives taken while breastfeeding will lead to very low levels in breast milk, and are unlikely to have a clinical effect in the infant.[12] **Breastfeeding women who are on antihypertensive medication should be advised to monitor their babies (especially those born preterm) for drowsiness, lethargy, pallor, cold peripheries or poor feeding.[3,12]**

Use of analgesics in breastfeeding women

Analgesics are among the most commonly used medications while breastfeeding and their use should be individualised to the breastfeeding mother and infant.

Paracetamol is the analgesic of choice while breastfeeding and is widely available as an OTC medicine.[40] Studies show variations in the concentration of paracetamol in breast milk, however the evidence suggests that it is very low and significantly less than the infant therapeutic dose of paracetamol.[3,28,29,37,38,40,41]

Non-steroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen, pass into breast milk in small amounts; ibuprofen is one of the analgesics of choice in breastfeeding women, especially for mothers of healthy infants born full-term.[3,16,28,29,37,40-42] Ibuprofen has a short half-life, is highly protein bound and is used in infants at doses much higher than those excreted in breast milk;[3,287] it is widely available OTC. An individual risk assessment needs to be taken if the mother is taking multiple medications or if the infant is unwell or premature.[42] Other NSAIDs such as diclofenac and celecoxib also pass into breast milk in small amounts and are considered compatible in breastfeeding women.[3,28,37,41] Naproxen has a longer half-life than other NSAIDs and there has been a report of a serious adverse reaction in an infant;[3,28,298] other agents may be preferred, especially for mothers of preterm or newborn infants.[3,28,29]

Aspirin is not recommended as an analgesic due to potential concerns regarding Reye's syndrome.[28,29,38,41] Low dose aspirin as an anti-platelet drug may be used with caution during breastfeeding if indicated, however the infant should be monitored for bruising.;[28,41,43] Breastfeeding, or low dose aspirin, should be discontinued if the infant develops a fever.[43]

Weak opioids: Neonates and young infants are particularly sensitive to the effects of opioid analgesics and are at most risk from adverse effects of opioids via breast milk due to their immature hepatic enzyme function, therefore extra caution should be taken in infants <2 months of age.[10,44] **Non-opioid analgesics should be used in breastfeeding mothers if possible.[28]** Codeine is a weak opioid that is converted into morphine by the cytochrome (CYP) P450 enzyme 2D6. There are genetic variants of CYP2D6 and some patients may be ultra-rapid metabolisers of codeine i.e. they metabolise codeine at a faster rate than others. Adverse effects have been reported in codeine-exposed breastfed infants (including apnoea, respiratory depression

and death) particularly in breastfeeding women who are ultra-rapid metabolisers of codeine.[3,5,44,45] As it is not possible to identify women who are ultra-rapid metabolisers,[3,44,45] some sources **contraindicate the use of codeine in breastfeeding women.**[44,45] The use of other weak opioids is suggested by some specialist sources for breastfeeding women, [3,29,44] however these have also been associated with adverse effects including drowsiness and respiratory depression in exposed breastfed infants.[28,44] If opioids are used, the lowest effective dose and shortest duration of therapy (2 to 3 days) should be prescribed in order to minimise the risk of adverse effects for both the mother and the infant (including infant drowsiness and central nervous system depression);[17,44] close medical supervision is required if use extends beyond 3 days.[44] **If opioid analgesics are taken by a breastfeeding woman, the infant should be monitored for sedation, breathing difficulties, constipation, feeding difficulties and poor weight gain.**[3,38,44]

Use of antibiotics in breastfeeding women

There are a number of useful national resources on the use of antibiotics in breastfeeding women including the HSE Antibiotic Prescribing website (www.antibioticprescribing.ie), which contains useful information on prescribing for conditions such as mastitis, postpartum endometritis and non-pregnancy specific infections that may occur in breastfeeding women. The HSE National Clinical Programme for Obstetrics and Gynaecology (www.hse.ie) has also published guidelines on antimicrobial safety in pregnancy and lactation which HCPs may find useful.[4]

Use of antihistamines in breastfeeding women

Antihistamines may be required by breastfeeding women for symptoms including pruritus and allergic rhinitis. Occasional use of small doses of antihistamines may be acceptable in breastfeeding women, however prolonged use may have effects on the infant and decrease milk production.[28] Non-sedating second-generation antihistamines such as cetirizine and loratadine, which do not readily cross the blood-brain barrier are preferred in breastfeeding women.[3,28,47,48] The older, first generation antihistamines (chlorphenamine and diphenhydramine) should be used with caution in breastfeeding mothers as they are sedating.[3,28,29,47] Bed-sharing with the infant is not recommended for parents who are on sedating antihistamines.[29,48] **Infants should be monitored for signs of excessive irritability, jitteriness and drowsiness.**[47]

Over-the-counter (OTC) Medicines

Lactating women should seek advice prior to taking OTC medicines. The use of combination OTC products (including combinations of paracetamol with caffeine, diphenhydramine, phenylephrine or pseudoephedrine) should be avoided especially in mothers of newborn infants.[40] Some OTC medicines (e.g. pseudoephedrine, phenylephrine and diphenhydramine) may decrease milk production.[28,40]

SUMMARY

Many medicines can be used in breastfeeding women. Table 3 summarises the key points about medicine use in breastfeeding.

Table 3: Key points about breastfeeding and medications[2,3,17,19]

- Most commonly used medicines can be used in breastfeeding women; it is rare that a breastfeeding mother needs to discontinue breastfeeding to take a medicine
- Breastfeeding women should avoid using medicines that are not necessary, e.g. over-the-counter medicines, herbal medicines
- The infant should be evaluated for risks from exposure to medicines via breast milk; neonates (and particularly premature infants) are at greater risk
- Medicines with high molecular weights, short half-lives, high protein binding and low oral bioavailability are preferred in some instances
- Older medicines for which there are published data are preferred, however it is important to choose medicines that will be effective in the mother
- Medicines that are licensed for use in infants do not generally pose a risk via breast milk
- Infants exposed to medicines via breast milk should be monitored for unusual signs or symptoms
- Multiple medicine regimens may pose an increased risk especially when adverse effects such as drowsiness are additive
- If the RID is <10%, most medicines are considered relatively safe to use, however this is dependent on the type of medicine and should not be used alone to evaluate risk
- Older children that are breastfed less frequently (e.g. once or twice daily) are at very low risk
- Discussions about the safety of medicines in breastfeeding should be held as early as possible in women with chronic conditions (e.g. depression, hypertension), ideally before conception or early in pregnancy
- Up to date information on use of medicines in lactating women is readily available; no single resource is totally comprehensive

There are several information resources available for HCPs on the use of medicines in breastfeeding women (see Table 4). It is important to bear in mind that no single information resource is totally comprehensive.

Table 4: Useful information resources on use of medicines in breastfeeding

- **Health Products Regulatory Authority:** The SmPC has prescribing information on lactation; it is generally regarded as being conservative in terms of its advice (www.hpra.ie)
- **HSE Antibiotic Prescribing website:** Includes guidelines for prescribing antimicrobials in lactation (www.antibioticprescribing.ie)
- **National Clinical Programme for Obstetrics & Gynaecology:** Clinical guideline available on antimicrobial safety in pregnancy and lactation (https://www.hse.ie/eng/about/who/cspd/ncps/obstetrics-gynaecology/resources/national-clinical-guidelines/ and www.rcpi.ie)
- **UK Drugs in Lactation Advisory Service (UKDILAS):** Monographs on use of medicines in lactation published by the UKDILAS which are available on the Specialist Pharmacy Service website (www.sps.nhs.uk)
- **LactMed:** US database which includes monographs on the safety of medicines in breastfeeding (https://www.ncbi.nlm.nih.gov/books/NBK501922/)
- **E-Lactancia:** This is a Spanish website with an English language version provided. It has a wide coverage of medicines with succinct entries and some monographs have short additional notes. Suitable alternative therapies are suggested where available (http://www.e-lactancia.org/)
- **Hale's Medications & Mothers' Milk (Thomas Hale):** Textbook available to purchase
- **Association of Anaesthetists:** The Association of Anaesthetists published a guideline on anaesthesia and sedation in breastfeeding women in 2020 (https://anaesthetists.org/Home/Resources-publications/Guidelines/Anaesthesia-and-sedation-in-breastfeeding-women-2020).
- **The Breastfeeding Network:** This is a website that provides evidence-based and practical information for mothers who breastfeed; it has information leaflets on use of medicines in lactation (https://www.breastfeedingnetwork.org.uk/drugs-factsheets/)
- **Academy of Breastfeeding Medicine:** This website includes protocols (guidelines) aimed to facilitate best practices in breastfeeding medicine (https://www.bfmed.org/)

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